JEJUNAL BIOPSY IN ADULT CŒLIAC DISEASE AND ALLIED DISORDERS

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" Whether atrophy of the glandular crypts of the intestine be ever or always present, I cannot tell." Gee (1888).

THE group of disorders giving rise to disturbance of intestinal absorption in the absence of gross anatomical or pathological changes in the gastrointestinal tract, liver, or pancreas has been known by various names. Cœliac disease and tropical sprue have recognised clinical implications, but in temperate climates idiopathic steatorrhœa, non-tropical sprue, jejunoileal insufficiency, sprue syndrome, malabsorption syndrome or just " sprue " are used more for convenience than for any ætiological implication.

The cause of these disorders and their relation to each other has been uncertain.

Fairley (1936) believed that some cases of idiopathic steatorrhœa were the adult form of cœliac disease and that tropical sprue was a separate entity, while Thaysen (1932) and Bossak et al. (1957) concluded that they were manifestations of the same underlying disorder. There is, however, strong clinical and biochemical evidence that cœliac disease and idiopathic steatorrhœa, at least in some patients, are basically the same disease and that tropical sprue is a separate disorder. Furthermore, as a result of the investigational techniques now available, the group known as " idiopathic steatorrhœa " seems likely to consist of a number of ætiologically distinct entities. In particular a great advance was made possible by Shiner (1956) in developing a suitable method of obtaining peroral biopsies of the jejunal mucosa with a modification of Wood's gastric suction biopsy tube and by Crosby and Kugler (1957) with their biopsy capsule. Ulceration, inflammation, and atrophy of the small-bowel mucosa had been reported in tropical and non-tropical sprue, but such changes were regarded as inconstant, non-specific, and in any case largely due to portmortem autolysis (Thaysen 1932). This view was generally accepted until Adlersberg and Schein (1947) in necropsy material, and Paulley (1954) in specimens obtained at laparotomy reawakened interest by demonstrating distinctive structural changes in patients with " idiopathic steatorrhœa ". Now, with peroral biopsy many other workers (Doniach and Shiner 1957, Butterworth and Perez-Santiago 1958, Smith et al. 1958, Bolt et al. 1958, Shiner and Doniach 1959, Culver et al. 1959) have demonstrated definite histological abnormalities in the small intestine of patients with steatorrhœa.

These observations suggest that more than one pathological lesion may be responsible for the syndrome, but the clinical and ætiological significance of the varied findings has remained obscure. In an attempt to clarify the problem, the findings in the jejunal biopsies of 58 patients with " idiopathic steatorrhœa " are presented and are correlated with the clinical features, the hæmatological, radiographic and biochemical findings and the absorption of ^{58}Co vitamin B_{12}.

Material and Methods

The 58 patients under discussion fulfilled the diagnostic criteria of " idiopathic steatorrhœa " (Cooke et al. 1953) or " adult cœliac disease " (Cooke 1958). They have all been under regular observation for periods of from a few months to nineteen years. The patients have been selected at random from those attending the steatorrhœa clinic at the General Hospital, and include all those who have been seen for the first time recently. The majority of observations were made while the subjects were outpatients. Biopsies have also been performed on 65 subjects of comparable age-groups—normal medical students, patients with pernicious anæmia, iron-deficiency anæmia, steatorrhœa due to pancreatic disease, regional enteritis and enterocolitis, and miscellaneous disorders not associated with gastrointestinal disease. These have been used for purposes of comparison and for determining the normal structure of the jejunal mucosa.

Since 1956, serum levels of vitamin B_{12} (Meynell, Cooke, Cox, and Gaddie 1957), folic-acid-excretion tests (Cox, Meynell, Cooke, and Gaddie 1958) and D-xylose-excretion tests (Fowler and Cooke 1960) have been estimated in the majority of patients.

Technique

20 biopsies were performed by Dr. Shiner, and these include 10 in cases of " idiopathic steatorrhœa "; the remaining 103 biopsies have been obtained with a Crosby capsule (Crosby and Kugler 1957). Fluoroscopic confirmation of the position of the capsule was obtained in all but a few patients. The majority of specimens were obtained from the upper jejunum, very few from the third or fourth part of the duodenum. These were fixed immediately in formol saline, embedded in paraffin, and stained with hæmatoxylin and eosin. In addition, all biopsies taken with the Crosby capsule have been stained with the periodic-acid Schiff (P.A.S.) reaction and a portion of the specimen fixed in cold acetone and stained for alkaline-phosphatase activity by the coupling azo-dye method (Pearse 1953). Serial sections were examined to prevent misinterpretations due to tangential cuts through the mucosa.

In 4 patients the absorption of ^{56}Co vitamin B_{12} was measured by the fæcal excretion method of Heinle et al. (1952) following the oral ingestion of 0·8 μg. vitamin B_{12} containing 0·5–0·85 μg. ^{56}Co. In the remainder the technique of surface counting over the liver (Glass 1956, 1959) was used. The amount of vitamin B_{12} was 0·26–0·4 μg., containing 0·25–0·5 μC ^{58}Co and administered in 20 ml. distilled water following a twelve-hour fast and immediately after an intramuscular injection of carbachol 0·25 mg. (Mollin et al. 1957). Surface counts were made for at least five minutes before and on two occasions between six and ten days after the administration of the test dose. The resulting counts have been corrected for background radiation and decay and expressed as counts per minute per microcurie. The mean in 21 control subjects was 2814 (S.D. 801, range 1700–4600) counts per minute per microcurie. In 7 patients with pernicious anæmia, the mean was 287 (S.D. 141, range 0–405) counts per minute per microcurie, returning to the normal range when ^{58}Co vitamin B_{12} was administered with intrinsic factor: mean 2277 (S.D. 473, range 1500–2979).

Results

The clinical and laboratory findings are summarised in the accompanying table and in fig. 1. The histological findings in these 58 patients with " idiopathic steatorrhœa" can be classified into three groups.

Group I

In 27 patients the appearances were strikingly uniform (fig. 2).

The mucosa was of normal or reduced width, and the surface completely or almost completely flattened, and no normal villi were present. When present the villi appeared broad and short and tended to fuse together; elsewhere there was no suggestion of villus formation at all. Crypts of Lieberkühn were infrequent and widely spaced. The surface epithelium was grossly abnormal. The cells were low cuboidal or flattened; the intercellular borders and basement membranes were indistinct; the brush border was reduced in width and frequently not visible in the hæmatoxylin and eosin (H. & E.), P.A.S., and alkaline-phosphatase preparations; the cytoplasm was often vacuolated; the nuclei varied in size, shape, and degree of staining. There often numerous "nuclei" crowded together, some of which appear to be nuclear fragments and some infiltrated leucocytes while normal epithelial nuclei were infrequent. In the pits of the remaining crypts of Lieberkühn, the epithelial cells showed less abnormality, and a few mitoses could be seen. There were very few goblet cells in the surface epithelial layer,

SUMMARY OF CLINICAL AND LABORATORY FINDINGS

—	Group I	Group II		
		A	B	C
Total	27	12	8	7
Age (yr.) at onset ..	1–53	4–46	26–59	14–73
Major symptoms:				
A, diarrhœa, malaise, weight loss	26	12	..	..
B, anæmia	1	..	8	7
Bone-marrow:				
A, megaloblastic ..	4	2	5	7
B, normoblastic ..	3	1	..	..
Initial hæmoglobin (g. per 100 ml.) ..	7·0–16·3	10·0–14·0	4·8–7·8	3·2–10·3
Serum-vitamin-B_{12} less than 105 µµg.	4 (*27*)	6 (*12*)	4 (*4*)	1 (*7*)
Vitamin-B_{12} absorption normal	16 (*18*)	5 (*7*)	1 (*6*)	6 (*6*)
Achlorhydria	4 (*13*)	4 (*7*)	6 (*6*)	0 (*7*)
Steatorrhœa	27	12	8	5 (*7*)
Xylose absorption abnormal	10 (*10*)	4 (*7*)	3 (*4*)	6 (*7*)
Folic-acid-excretion test abnormal	15 (*15*)	7 (*7*)	4 (*5*)	4 (*5*)
Remission induced by gluten-free diet ..	8 (*11*)	6 (*9*)	..	..

Group I.—Patients with "flat" jejunal biopsy.
Group II.—Patients with "abnormal" villi in jejunum: A, patients in whom diarrhœa, malaise, and weight loss were the major features; B, patients in whom severe anæmia responding to vitamin B_{12} was the major feature; C, patients in whom severe anæmia responding to folic acid was the major feature.
Figures in parentheses refer to the total number in whom the test was performed.

although present in the tubules. The glandular tubules were normal or reduced in number, and often elongated and dilated. Paneth cells were present. In the lamina propria there was mild or moderately heavy cellular infiltration, consisting predominantly of plasma cells, with less numerous lymphocytes and eosinophils, a few macrophages, spindle cells, and occasional polymorph cells. Some interstitial œdema and lymphatic dilatation was present.

Immediately beneath the epithelial layer in some areas there was a narrow band of homogeneous eosinophilic material, which tended to separate the epithelial layer from the underlying lamina. In no instance was there any evidence of a hyaline

Fig. 1—Absorption of radioactive vitamin B_{12}.
Open circles: test performed with ^{58}Co vitamin B_{12}.
Closed circles: test performed with ^{58}Co vitamin B_{12} plus intrinsic factor.
The composition of groups I and II is described in the table.

band at the free surface of the cells, as was described by Schein (1947).

Although in 11 patients biopsy was performed during clinical remission and in 16 during the initial illness or during a relapse, the histological appearance was essentially the same.

The age of onset of symptoms in this group varied from early childhood to 59 years. In 8, symptoms commenced before the age of 10, and in 2 others between 10 and 20 years. The main presenting feature was diarrhœa, which had been present for at least two years before the patients were first seen. Only in case 20, a man aged 42, could it be stated that symptoms attributable to anæmia were the presenting features; there had been a severe attack of diarrhœa twelve months previously and a history of "tuberculous abdomen" at the age of 19. Glossitis at some time was common to all patients. Abdominal pain, however, except in the periods in which abdominal distension and hypokalæmia were present, was rare; in only 1 patient was pain a troublesome feature and without obvious cause. The blood picture was usually macrocytic with moderate anæmia. Only 7 had hæmoglobin concentrations of less than 10 g. per 100 ml. when first seen. Although the average period of observation in this group is nearly seven years, and all have had regular blood-counts, only 2 have subsequently had a hæmoglobin of less than 10 g. Since severe anæmia has not been a prominent feature only 7 sternal punctures were performed. Of these bone-marrows 4 were megaloblastic; the other

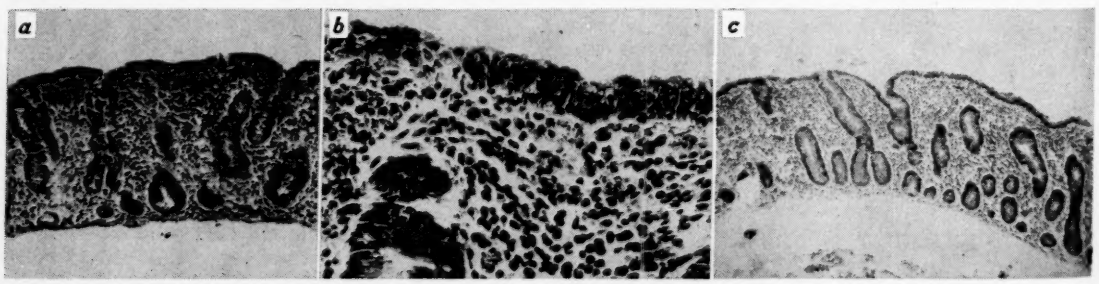

Fig. 2—Jejunal biopsy in group I: (*a*) Absence of villi, flat surface, disordered epithelium, and slightly increased cellularity of lamina propria (case I: H. & E. × 100); (*b*), epithelial surface in case 1, showing severe cellular disorder (H. & E. × 400); (*c*), "crypt" in case 2 (serial sections suggest that these are not true crypts) (H. & E. × 80).

3 were normoblastic, although 1 of these showed hypersegmentation of the nuclei and giant metamyelocytes. Hypoferræmia has been present in nearly all patients, and in many needed parenteral iron for correction. Steatorrhœa varying from 8 to 25 g. daily was present in all, and radiographic patterns of the small intestine were abnormal in all. D-xylose-excretion tests were abnormal in all 10 tested, but in 2 results were normal during subsequent remissions. Free hydrochloric acid was present in the gastric content in 9 out of 13 in whom it was sought, though in 3 of the 4 with achlorhydria histamine was not given. Folic-acid-excretion tests were abnormal in all 15 patients examined. In only 4 patients was a low serum level of vitamin B_{12} encountered. In 1 this was during pregnancy and righted itself following confinement. In another, a man aged 38 who has only recently come under observation, it was associated with low levels of serum-iron and normal absorption of ^{58}Co vitamin B_{12}. The other 2 have attained normal serum levels of vitamin B_{12} with treatment—1 with intramuscular iron and the other with a gluten-free diet. Absorption of ^{58}Co vitamin B_{12} has been studied in 18 patients. In 16 absorption was normal. In 2 absorption was poor and was unaltered by the addition of intrinsic factor. In the only one tested, absorption was not improved by the addition of calcium. Both these patients had been receiving injections of vitamin B_{12} for some time when the absorption studies were made. Only 11 patients were treated with a gluten-free diet, and, of these, 3 were unable to adhere to the diet. 8 patients had satisfactory clinical remissions. Of the remaining 16 patients 1 died of a pulmonary infection; the others regained good health with the administration of oral folic acid or parenteral iron, often maintaining this state for years without any therapy.

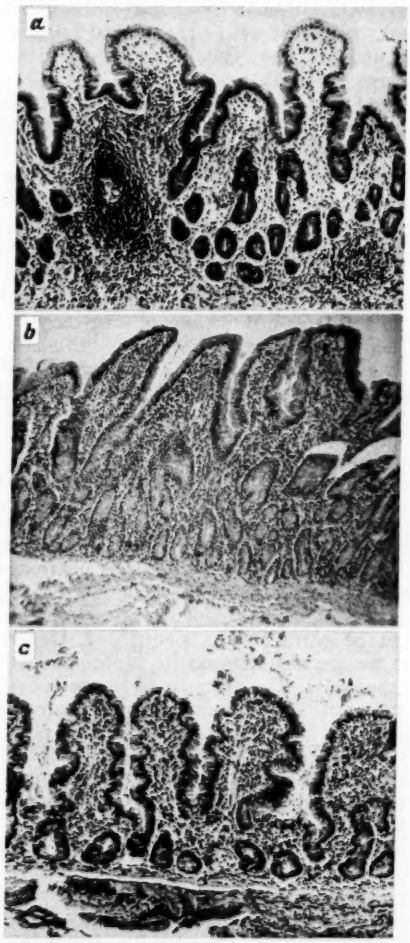

Fig. 3—Jejunal biopsy in group II: (*a*), villi abnormally shaped, epithelium only slightly abnormal, moderate cellular infiltration (case 29: H. & E. × 100); (*b*), abnormally shaped villi, with less severe epithelial disorder and cellular infiltration (case 35: H. & E. ×100); (*c*), villi short and broad, surface epithelium abnormal, and moderate cellular infiltration of lamina propria (case 40: H. & E. ×100).

Group II

In 27 cases the microscopic appearances were considered to be abnormal (fig. 3). but to differ from the appearances seen in group I. In particular the absence of villi and flattening of the free surface were not found. Although individual specimens showed considerable variation and so were not quite such a homogeneous histological group as group I, they did show sufficient similarities to warrant inclusion as a separate group.

In a few instances the mucosa was thicker than normal, though in most it was of approximately normal or reduced width. Villi were present in all specimens, but abnormal in size, shape, and structure; they were commonly short, occupying less than half the total width of the mucosa; many were broad, particularly at the base, and squat. The appearance of the villi varied considerably between the individual sections; in some a few comparatively normal villi were present. The surface epithelium varied considerably in the degree of epithelial change, but this was never so severe as seen in group I, and did not always parallel the extent of abnormality of villous architecture or cellular infiltration of the lamina propria. The glandular tubules showed little elongation or dilatation. Goblet cells were often numerous.

In the lamina propria there was mild, moderate, or heavy cellular infiltration. In a few instances plasma cells were numerous, but in most the cells were mostly lymphocytes, histocytes, and spindle cells, with less numerous plasma cells, a few eosinophils, and occasional polymorphs. This cellular infiltration tended to be more unevenly distributed than in group I, and was heavier in the deeper parts of the mucosa than in the villi themselves, and in some cases formed very dense follicles. Often it extended into and through the muscularis mucosæ, and into the epithelium. In case 36 an area of superficial inflammatory ulceration was present.

In 17 patients these changes were pronounced, with much disturbance in the architecture of the villi, moderate epithelial disorder, and moderate or heavy cellular infiltration. In 10 there was less disturbance, the main features being some shortening and broadening of the villi with mild cellular infiltration.

The major clinical manifestations in the patients with "abnormal villi" fell into two main categories—(1) malaise and mild diarrhœa, and (2) severe anæmia of relatively short duration. The 12 patients in whom malaise and diarrhœa were main symptoms resembled the patients with the "flat" biopsy appearance of group I, but on more detailed analysis points of difference could be demonstrated in the majority. The age at onset was similar (4 to 46 years); in 3, symptoms started before the age of 10, and in 2, between 10 and 20. The duration of symptoms varied from three months to twenty years; in half it was between one and two years. In 5 patients colicky abdominal pains were a feature, resulting in laparotomy in 2. In both these patients the small bowel was slightly œdematous and hyperæmic, and the mesenteric lymph-nodes

were enlarged, while in 1 there were adhesions about the lower ileum. Steatorrhœa was present in all. Radiographically the small intestine was abnormal in all but 1 of the patients. Similarly, the folic-acid-excretion test was abnormal in all except case 35, which has been reported elsewhere (Cox et al. 1958). D-xylose excretion was impaired in 4 and normal in 3. Low levels of serum-iron were encountered in all but 1. Low-serum-vitamin B_{12} levels were present in 6 of the 12 patients. Of these 6 patients 4 were studied with ^{58}Co vitamin B_{12}. 2 had normal absorption, and in 2 the absorption was impaired but was corrected by the addition of intrinsic factor. 3 further patients with normal levels of serum-vitamin-B_{12} had normal absorption of ^{58}Co vitamin B_{12}. Only 3 patients (cases 29, 30, and 37) had had a hæmoglobin of less than 10·0 g. per 100 ml. In case 29, who had megaloblastic anæmia, complete response was effected with vitamin B_{12}. Case 30 responded satisfactorily to parenteral iron. Case 37, with very slight evidence of megaloblastic erythropoiesis, responded well to a gluten-free diet. Of the other 2 patients in whom sternal puncture was performed, 1 had megaloblastic erythropoiesis and responded completely to injections of vitamin B_{12}. Of the 7 patients in whom gastric function was investigated, 5 had no free acid in the gastric juice. A gluten-free diet had been prescribed in 9 patients. 6 patients improved considerably on this diet, but in some improvement could be attributed to coincident therapy with vitamin B_{12}. In cases 37 and 38, however, complete clinical, hæmatological, and biochemical remission had been obtained though the folic-acid-excretion test was still abnormal in both. In these 2 patients there was no detectable difference, other than the biopsy findings, from group I. In case 28 no improvement resulted on a gluten-free diet for nine months, but definite improvement was subsequently obtained with steroid therapy. In the other 2 patients (cases 30 and 34) improvement was noted initially. In 1, final assessment is awaited; and in the other the diet was discontinued after a few months' trial with only moderate improvement, though subsequently clinical remission was attained on ordinary diet.

The 15 patients presenting with severe anæmia had had symptoms for from a few weeks to a year before coming under treatment. Episodes of diarrhœa had been common but relatively recent, and never as troublesome as in the other patients that have been considered. Of these cases, 8 showed a prompt clinical and hæmatological response to therapy with vitamin B_{12} and only maintained this with regular treatment. The ages at time of diagnosis were 26, 36, 37, 47, 50, 53, 60, and 65 years. 5 of the 8 patients were seen by us before treatment; in each the bone-marrow was megaloblastic. The others had already received treatment elsewhere, and the bone-marrow had not been examined. The initial hæmoglobin concentration in the blood of these 5 varied from 5 to 7 g. per 100 ml. In the 7 patients tested, free hydrochloric acid was absent from the gastric contents. In 4 of the 7 patients examined, ^{58}Co vitamin B_{12} was not absorbed normally until intrinsic factor was administered. Case 40, though having a serum level of vitamin B_{12} of 75 μμg. per ml., absorbed ^{58}Co vitamin B_{12} normally, and furthermore responded normally and completely to therapy with vitamin B_{12}. Case 47, whose anæmia has responded well to vitamin B_{12} but in whom the initial level of serum-vitamin-B_{12} and bone-marrow appearances were not known, had subnormal absorption of ^{58}Co vitamin B_{12}. The 7th patient (case 41) had severely impaired absorption which was not corrected by the addition of intrinsic factor. All 7 patients tested had abnormal fæcal excretion of fat, varying from 7 to 14 g. per day. The folic-acid-excretion test was abnormal in 4 of the 5 patients tested, and xylose excretion was abnormal in 3 of the 4 tested.

The other 7 patients responded well to folic acid or citrovorum factor. In these the ages at onset were 14, 17, 32, 32, 39, 42, and 73 years. 5 had steatorrhœa varying from 8 to 12 g. per day; but in 2, aged 14 and 32, despite the history of diarrhœa, no steatorrhœa was demonstrated. They are included here, however, because of the abnormal xylose and folic-acid excretion tests and abnormal jejunal mucosa. All had free acid in the gastric contents. 6 patients when first seen had hæmoglobin concentrations of 3–7 g. per 100 ml. All 7 had megaloblastic bone-marrow. All absorbed ^{58}Co vitamin B_{12} normally. Though levels of serum-iron were within (or above) normal range at the time of their megaloblastosis, all showed evidence of iron deficiency before return to normal blood-counts. 4 of the 5 patients examined had abnormal folic-acid-excretion tests. The xylose-excretion test was abnormal in 4 of the 5 patients tested. In the 5th (case 54) it was normal at a time when the patient was in clinical and hæmatological remission and had been under intermittent therapy for fifteen years.

In none of these 15 patients presenting with anæmia was a gluten-free diet prescribed. This was not necessary for control of bowel symptoms, and health and weight were rapidly regained with hæmatinics only.

Group III

There were 4 patients who presented with anæmia and diarrhœa to whom the diagnosis of idiopathic steatorrhœa had been applied and in whom the jejunal biopsies had proved to be normal.

3 of the 4 patients had histories of long-continued iron loss—either menorrhagia or from œsophagitis in association with a hiatus hernia. In 2 steatorrhœa had been intermittently present. In all, the administration of iron parenterally has led to cessation of abdominal symptoms. This group is still under investigation and will not be considered in further detail at present.

Discussion

In the past few years, the functions of the various segments of the bowel have become more clearly defined. Hence, disturbances of folic-acid, xylose, and iron absorption can be expected when the jejunum is involved in disease processes, while production of the intrinsic factor fails when the gastric mucosa is atrophied. Despite comments to the contrary, vitamin B_{12} is absorbed more distally, in the ileum. The main site of fat absorption in the man is still debatable; for experimental observations by Bergström et al. (1957) suggest that it takes place in the first 50–100 cm. of the small intestine, whereas clinical observations in regional enteritis or following surgical resection of the gut point to the ileum as an important site of fat absorption. Hence lesions of differing ætiology affecting the upper small intestine may well be associated with essentially similar clinical pictures and cause serious difficulties in differential diagnosis. The converse is also true—that conditions of the same ætiology can give rise to differing clinical pictures according to the length and area of intestinal tract involved.

As the result of our studies, we believe that at least two and probably three ætiologically different disorders are responsible for "idiopathic" non-tropical steatorrhœa. The most striking and homogeneous histological group

in our series is group I, with "flat" jejunal mucosa; and we consider that this represents an ætiological group separate from group II, in which the mucosa shows "abnormal villi". Analysis of the clinical and biochemical features in the two groups seems to support this belief.

It might be argued that, as only single biopsies were obtained with the Crosby capsule, such specimens are not truly representative. Second biopsies have been obtained from only 5 patients, at an interval of at least a year after the first biopsy. In each case the appearances do not differ significantly from those in the first. While repeat biopsies are being obtained in furtherance of this study, the results so far seem to justify regarding the patients with the "flat" biopsies as a homogeneous group, and this hypothesis is unlikely to be upset by a larger number of observations.

It might also be argued, as Himes and Adlersberg (1958) suggest, that the "flat" biopsies were the end-result of a pathological lesion which in the earlier or less severe stage would have had an appearance similar to those with "abnormal villi". Alternatively, if regeneration occurred in a "flat" mucosa, bizarre and abnormal villi would result. There does, however, appear to be strong evidence in our patients that this is not so. 3 patients in group II have had the disease for fifteen to eighteen years. Case 54 was first seen seventeen years ago with severe anæmia and has had hæmatinic therapy ever since without ever attaining complete remission. In case 30 symptoms started at the age of 4, and, although she is now well at the age of 22, she has had numerous severe relapses, only seeking treatment when compelled to do so. Case 20 has had many episodes of diarrhœa and severe megaloblastic anæmia over a period of fifteen years and was at the time of each of his two biopsies in relapse. Neither time nor lack of treatment appeared to have produced a "flat" biopsy in these 3 patients.

On the other hand, 2 patients in group I were seen recently at the age of 39 and 53 with relatively mild symptoms which had been present for only a year, and yet each had a "flat" biopsy. 6 patients in group I had been in good health with no symptoms for periods of five to ten years when the biopsy was performed. In 4, this was the result of treatment (gluten-free diet in 3, folic acid in 1) and in 2 of no treatment at all other than some restriction of fatty foods. All 6 have "flat" biopsies, with absence of villi and a disordered epithelium. These and similar observations suggest that regeneration in this type of lesion does not occur to any significant degree, although complete clinical remission may occur. Similar observations on the improvement in function despite the persistence of the histological changes have been made by Shiner and Doniach (1959).

The majority of published pictures and descriptions fit the appearances that are found in group II. As yet no published evidence points to transition from the abnormal villi to the biopsies with absent villi, seen in our group-I patients. Butterworth and Perez-Santiago (1958) described a case in which the patient had had several episodes of severe anæmia and intermittent therapy and which still showed abnormal villi and no "flat" biopsy at the end of nine years. Butterworth and Perez-Santiago (1958) also found that in a patient with "tropical sprue" the abnormal villi returned to near normal with folic-acid therapy. A similar finding had previously been reported by Shiner and Doniach (1959). The only 2 patients with tropical sprue whom we have examined had had severe megaloblastic anæmia twelve to fourteen years previously and had been well without therapy for eight to ten years. In both instances jejunal biopsies were essentially normal.

The occurrence of virtually normal absorption of ^{58}Co vitamin B_{12}, the infrequent finding of low serum levels of vitamin B_{12}, and the relatively low incidence of severe anæmia and of severe abdominal pain are further evidence that the disorder in the patients of group I is a distinct entity. The findings contrast strikingly with the findings in group II, the more so if the lesions of group II are regarded as the precursor to the development of a "flat" biopsy.

Good clinical responses were obtained with a gluten-free diet in both the patients with "flat" biopsies and those with abnormal villi. Since it has been suggested that "gluten-induced enteropathy" is a distinct clinical and ætiological disorder (Frazer 1959) the fact that satisfactory results were obtained in both groups could be regarded as evidence that the ætiology was the same in both despite the pathological differences. There have, however, been a few case-reports of patients with secondary steatorrhœa who have been benefited by a gluten-free diet (Finlay and Wightman 1956, Forshaw 1958, Krainick 1958, Chan Jon Chu 1958, Nassim et al. 1959). It cannot be deduced from this that gluten-free diet does not have a specific effect in cœliac disease; but it does apparently have a powerful non-specific effect in some intestinal disorders, and probably so acts in some patients with abnormal villi. For example, in case 31 the intestinal symptoms have been satisfactorily controlled and the patient's general health improved; but even so his stools still contain 8 g. of fat per day, his serum level of B_{12} is low, and intrinsic factor is absent after five years on a gluten-free diet.

The pathogenesis of the lesion in group I is not known. The most prominent features are the absence of villi, the disordered epithelium with evidence of cell degeneration and regeneration, and the predominantly plasma-cell infiltration of the lamina propria. Evidence is accumulating that the basic defect in cœliac disease is enzymatic or cellular. It has previously been suggested that such a defect in the epithelial cells would lead to all the morphological changes seen in the biopsy specimens (Himes and Adlersberg 1958). Such an explanation would be consistent with the changes seen in our group-I biopsies, but further histochemical and biochemical studies are necessary to elucidate this problem.

The histological appearances in group II are less uniform than those in group I. Many have the characteristics of a chronic inflammation (fig. 3a). In others (fig. 3b) the major change is in the appearance of the villi, with less severe epithelial disorder or cellular infiltration. Whilst these latter appearances may represent a further difference in ætiology, they could well be a later or less active stage of a similar inflammatory process. We therefore suggest that in many of this group the small-bowel lesion is a form of chronic jejunitis with various degrees of mucosal atrophy. The findings at laparotomy in the 2 patients of this group tend to support this hypothesis of an inflammatory lesion. It is noteworthy that in the only patient in group I who has had a laparotomy, the small bowel was found to be atonic and dilated, and the mesenteric lymph-nodes were not enlarged.

The biopsy appearances are in general similar within each of the three subgroups of group II. This does not, however, necessarily denote a common basic ætiology;

indeed certain of the differences in clinical and biochemical features suggest that the distinction may not be wholly explicable simply in terms of severity or the amount of intestinal tract involved. The patients whose severe megaloblastic anæmia responded to vitamin B_{12} do clearly differ from those whose anæmia responded to folic-acid substances. In 4 of the former group vitamin-B_{12} absorption studies indicated a deficiency of intrinsic factor, and gastric biopsy revealed chronic atrophic gastritis in each. In those responding to folic acid, the presence of free gastric hydrochloric acid and normal absorption of ^{58}Co vitamin B_{12} indicate that the gastric mucosa is virtually normal, although histological confirmation of this has not yet been obtained. It might be argued that the difference between these two groups is merely that in one the lesion is more extensive and involves the stomach as well as the jejunum. If this were so, however, one should expect to find that the vitamin-B_{12}-deficient group would also manifest folic-acid deficiency, but this has not been the case. It is also of interest that one of the patients whose anæmia responded to vitamin B_{12} had a normal absorption of ^{58}Co vitamin B_{12}. In this patient (case 40), a man of 39, gastric biopsy revealed normal mucosa. The mechanism of the vitamin-B_{12} deficiency in this case is not yet clear; it is certainly different from the other patients in this group, and further study may reveal that the basic ætiology is also different. The patients with vitamin-B_{12} deficiency and intrinsic factor defect must also cause difficulty in differentiation from addisonian pernicious anæmia unless intestinal absorption studies and jejunal biopsies are performed. Similar examples of steatorrhœa and lack of intrinsic factor, though without biopsy studies, have been recorded by Mollin et al. (1957), Jarvinen and Latvalahti (1958), and Williams et al. (1958).

Jejunal-biopsy appearances essentially similar to those which we have described in group I have been described in cœliac disease (Sakula and Shiner 1957, Brandborg et al. 1959). Rubin et al. (1958) believe that the findings in cœliac disease and "idiopathic sprue" are identical, basing their opinion on 9 juvenile cœliacs and 17 adult patients. At the Children's Hospital, Birmingham, biopsies have been performed on 26 children with steatorrhœa aged 2–14 years: 24 who had the clinical features of cœliac disease had histological findings similar to those described in our group I (Cameron 1960). We suggest that in future the name cœliac disease or adult cœliac disease should be applied only to those patients with a "flat" jejunal biopsy. For the moment, there is no suitable designation for those with "abnormal villi", though "jejunitis", "non-tropical sprue", or simply "sprue" may each have its advocates.

Of the patients with "flat" biopsies and those with abnormal villi, a few failed to absorb vitamin B_{12} even with the addition of intrinsic factor. Oxenhorn et al. (1958) found that this was so in nearly all the 25 patients that they studied. As was suggested by Mollin et al. (1959) this failure to absorb vitamin B_{12} with the addition of intrinsic factor should indicate extension of the lesions down the intestinal tract. Such lesions have been reported by Thaysen (1932), Salvesen and Skogrand (1957), Mollin et al. (1959), and Shiner and Doniach (1959), but there has been little published evidence on the frequency of normal microscopic appearances in the ileum. With the reservations necessary when dealing with postmortem findings, we believe that the distal small intestine in some of our cases examined at necropsy was normal, as was suggested in the present series by our findings with ^{58}Co vitamin B_{12}. Furthermore, since similar findings with regard to absorption of vitamin B_{12} occur in regional enteritis, the fact that such findings are also encountered in both the patients with "flat" biopsies and those with abnormal villi does not necessarily signify that the two groups are ætiologically identical.

The apparent dissociation between the absorption of vitamin B_{12} and fat in the patients with "flat" biopsies and in those with the abnormal villi and megaloblastic anæmias responding to folic acid is not readily explained; but possibly the observation of Borgström et al. (1958) that fat is absorbed in the first 50–100 cm. of the small intestine is relevant. Nevertheless, it might have been expected that the lower ileum would take over fat absorption, since in regional enteritis excision of the lower ileum often leads to steatorrhœa.

Summary

Jejunal biopsies have been performed on patients with "idiopathic steatorrhœa" or "adult cœliac disease".

In 27 patients the appearances were uniform, with absent villi, epithelial disorder, and mild to moderate cellular infiltration, mainly with plasma cells.

In 27 the villi were present but abnormal in shape, the epithelial disturbance was less severe, and the cellular infiltration was usually heavier.

In 4 patients the villi were normal.

Clinical features and laboratory findings indicate that the cases with absent villi are ætiologically distinct from the rest. It is suggested that this group be called cœliac disease or adult cœliac disease, and that these terms be confined to patients with this lesion.

The second group with abnormal villi probably represents more than one ætiological disorder. For this group there is at present no satisfactory name.

We are grateful to Dr. M. Shiner for introducing us to jejunal biopsy and for allowing us to include the results thus obtained; the physicians of the General Hospital for allowing us to investigate their patients, and Dr. C. F. Hawkins for referring cases 29-32 for further study; and lastly, but by no means least, to the many patients who willingly gave their time to allow these investigations to be carried out. We are indebted to the endowment research fund of the United Birmingham Hospitals for a grant for equipment and for financial support to one of us.

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THYROIDITIS AND CIRRHOSIS OF LIVER

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THE question whether thyroiditis may be associated with cirrhosis of the liver has been widely discussed (Luxton and Cooke 1956, Roitt and Doniach 1958, Anderson et al. 1959a and b, Doniach et al. 1959) but very few patients with both diseases have been described.

We present three instances of death from liver failure in women who had chronic thyroiditis.

Case-reports

Case 1.—A married woman, born in 1903, had had jaundice in 1911 but otherwise had been healthy until 1954 when she attended the Cardiff Royal Infirmary because of a swelling in the neck. She remembered that she had had a goitre for some years between the ages of 10 and 19. This had gradually subsided, but six months before being seen in hospital she had noticed a return of the swelling and it was gradually increasing in size. There were no other symptoms.

Fig. 1—Case 1: microscopic appearance of thyroid gland (×100).

The patient was of normal build without any evidence of hypothyroidism or thyrotoxicosis. Abnormal physical findings were confined to the neck where there was diffuse firm enlargement of the thyroid gland, particularly on the right side. Blood-pressure (B.P.) 145/90 mm. Hg. Hb 10·6 g. per 100 ml., serum-cholesterol 345 mg. per 100 ml. She was admitted to hospital, and on Aug. 6, 1954, subtotal thyroidectomy was performed by Mr. D. B. E. Foster. The appearance of the gland at operation suggested chronic thyroiditis of Hashimoto's type, and the histological report (Dr. A. G. Heppleston) was: "the features are those of Hashimoto's disease with considerable squamous metaplasia of the surviving epithelium" (fig. 1). Recovery from the operation was uneventful, and the patient was given thyroid extract gr. 1 daily.

She was next seen at the Cardiff Royal Infirmary in 1957. She had had epigastric pain for three years, and loose pale motions and jaundice for six months. The urine had been dark. Jaundice had varied in intensity and was not very noticeable when she was examined. No thyroid tissue could be seen or felt. There were spider nævi on both hands and one on the face, and there were bruises on the legs. The liver was enlarged to 2 in. below the costal margin and was not tender; the spleen was palpable. There was no œdema or ascites. B.P. 130/75.

The blood-count was normal (Hb 11·8 g. per 100 ml., white cells 4900 per c.mm.) but the erythrocyte-sedimentation rate (E.S.R.) was raised (43 mm. in the first hour, Wintrobe). Serum-protein 7·6 g. (albumin 2·9 g.) per 100 ml.; electrophoretic pattern showed increased γ-globulin. Serum-bilirubin 2·5 mg. per 100 ml., serum-alkaline-phosphatase 25·2 King-Armstrong (K.-A.) units per 100 ml. Thymol turbidity 20 units and thymol flocculation 4+.

During the latter half of 1957 the patient's condition did not change, but in 1958 the jaundice increased and she began to feel unwell. In view of this and the possibility that Hashimoto's disease might be related to cirrhosis it was decided to seek the opinion of Dr. Sheila Sherlock. The patient was transferred to the Hammersmith Hospital and we are indebted to Professor Sherlock for the results of the following additional investigations:

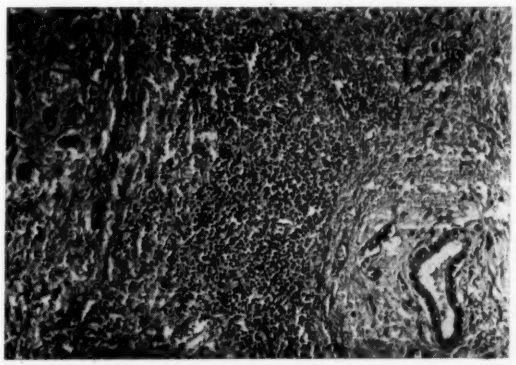

Fig. 2—Case 1: microscopic appearance of liver (×100).

Liver biopsy: fibrosis, some distortion of pattern; cirrhosis; liver cells swollen, vacuolated, and bilestained; portal tracts heavily infiltrated with lymphocytes—an active cirrhosis. Thyroglobulin precipitin test positive. Complement-fixation strong positive. Tanned-red-cell agglutination strong positive. Radio-iodine test: "T" factor 1·6 (normal 2·8—13).

While at Hammersmith Hospital the patient was given prednisolone, but this was stopped because she felt unwell and œdema developed. She was then given triamcinolone 4 mg. b.d. and went home two weeks later.

Three months later, in November, 1958, she was readmitted to the Cardiff Royal Infirmary. She felt extremely unwell and had had œdema of the ankles continuously. A month before readmission the jaundice had become worse; her abdomen began to swell and she developed diarrhœa, a sore mouth, and dyspnœa on exertion. During this month she had had no further triamcinolone. She had been having a high-protein, low-salt diet, mersalyl twice weekly, and thyroid extract gr. 1 twice daily.

The patient looked thin and ill and was deeply jaundiced. There was œdema of the legs and over the sacrum; there was also severe ascites, and the liver and spleen were enlarged.

The serum-protein was now 6·0 g. (albumin 1·6 g.) per 100 ml., serum-alkaline-phosphatase 34 K.-A. units per 100 ml., and serum-bilirubin 14·3 mg. per 100 ml. Thymol turbidity

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7 units and thymol flocculation 2+. Serum-electrolytes were normal (sodium 137 mEq., potassium 3·3 mEq., and chloride 103 mEq. per litre).

Three days after admission the patient became drowsy and had severe diarrhœa. This continued and her condition deteriorated gradually. She became comatose on the fourteenth day after admission and died two days later.

Postmortem Findings

The peritoneal cavity contained a large amount of ascitic fluid, and the intestinal tract contained much altered blood originating from œsophageal varices. No recognisable thyroid tissue was found, and the fragments of tissue taken for section consisted only of lymphoid and fibrous tissue. The liver weighed 1100 g., was of firm consistence, and was traversed by a network of grey fibrous tissue in which were embedded greenish nodules of liver tissue. Histologically (fig. 2) there was diffuse fibrosis with nodular hyperplasia of liver parenchyma. The fibrous tissue showed widespread and intense infiltration with plasma cells and lymphocytes. Bile-duct proliferation was present round the periphery of most nodules, and intracanalicular bile thrombi were present.

Case 2.—A married woman, born in 1901, had diphtheria when she was a child, and in 1927 both her ovaries were removed because of persistent abdominal pain two years after the birth of a child.

In 1938 she noticed that her abdomen had become swollen quite suddenly. Soon after this her limbs and face became puffy and she gained weight. At the same time she noticed that her urine was frothy and scanty. She was admitted to hospital where subacute nephritis was diagnosed (no notes are available for this admission). At the time of discharge she was still œdematous; and this œdema persisted, varying in degree.

In 1949 she began to have attacks of angina pectoris. These increased in severity and duration and led to her admission to hospital in 1952. At that time she was noted to be pale, obese, and œdematous. The ankles and face were puffy and the eyebrows scanty. The skin was thick, dry, and pigmented and the nails were brittle. There were numerous bruises on the skin. The thyroid was not enlarged, nor were the liver or spleen palpable. B.P. 210/130.

The basal metabolic-rate (B.M.R.) was −20%, and serum-cholesterol 450 mg. per 100 ml. A radiograph of the chest showed that the heart was enlarged and an electrocardiograph, which was of normal voltage, showed left axis deviation and myocardial ischæmia. Serum-protein 7·6 g. (albumin 4·7 g.) per 100 ml. The urine contained no protein or abnormal deposit.

Myxœdema with coronary atherosclerosis was diagnosed, and the patient was given thyroid extract gr. $^1/_{10}$ daily, which was gradually increased to gr. 1 t.d.s. She improved rapidly at first, but a month after admission had a coronary occlusion which was followed by mild heart-failure. Treatment with thyroid extract was interrupted for three weeks and then resumed with gr. $^1/_{10}$ daily which was increased to gr. 1 q.d.s. After being in hospital for four months the patient went home feeling much better. She then had no œdema, and had lost 3 st. in weight. B.M.R. +10%. Serum-cholesterol 279 mg. per 100 ml.

Her condition improved gradually until December, 1952, when she began to have attacks of epigastric pain followed by vomiting. These occurred at night and were accompanied by a desire to defæcate. In January, 1953, she became jaundiced and noticed increasing thirst. Her urine was dark and motions pale. Despite a return of the ankle œdema she began to lose weight rapidly. She was readmitted on Jan. 30, 1953.

The patient was found to be jaundiced and lethargic. Her face was puffy but there was no œdema elsewhere. The liver was enlarged to 5 in. below the costal margin, but the spleen was not palpable. B.P. 105/50.

Serum-protein 7·3 g. (albumin 3·7 g.) per 100 ml., serum-alkaline-phosphatase 34·2 K.-A. units per 100 ml., serum-bilirubin 21·6 mg. per 100 ml., thymol turbidity 1 unit, thymol flocculation 0, zinc turbidity (Kunkel) 4 units, prothrombin index 1·6. The blood-count was normal (Hb 13·4 g. per 100 ml., white cells 9000 per c.mm.), and serum-cholesterol 295 mg. per 100 ml.

Condition deteriorated rapidly and within three days it was apparent that her liver was decreasing rapidly in size. Jaundice increased and six days after admission she became comatose and died.

Postmortem Findings

There were ulcerated œsophageal varices, and the gastro-intestinal tract contained a considerable amount of altered blood. The liver weighed 1780 g. and was finely granular. Microscopically the appearance of the liver closely resembled that in case 1 except that the infiltration of the fibrous tissue with lymphoid cells was less intense and some eosinophil leucocytes were present. There was no necrosis of liver parenchyma. The thyroid gland consisted of a network of fibrous tissue in which were embedded nodules of thyroid parenchyma. These were composed of small acini lined by eosinophilic and pleomorphic cells. There was little colloid in evidence. Extensive accumulations of lymphocytes and plasma cells surrounded and infiltrated the nodules. The appearances were those of chronic thyroiditis of Hashimoto type.

Case 3.—A married woman, born in 1892, had been healthy until February, 1948, when she had a small hæmatemesis. In September, 1948, she had three further hæmatemeses and had to be admitted to hospital. She was pale and shocked. B.P. 100/60, pulse-rate 100 per min. Abnormal physical signs were confined to the abdomen; her spleen was enlarged. After blood-transfusion her condition rapidly improved, and she then said that she thought she had had hæmatemeses in about 1917 and 1923. Radiographic examination showed that she had œsophageal varices. Liver-function tests were substantially normal (serum-protein 7·5 g. (albumin 4·5 g.) per 100 ml., serum-bilirubin 0·5 mg. per 100 ml., serum-alkaline-phosphatase 12 K.-A. units per 100 ml., thymol turbidity 6 units).

In 1952 the patient again had a hæmatemesis and was readmitted to hospital. There was no comment on the thyroid gland, but her spleen was still enlarged. Liver-function tests were repeated with results similar to those found in 1948.

She then remained well until June, 1955, when she was again admitted to hospital having had three hæmatemeses. On examination she was obese and pale but not shocked. Her appearance was "heavy, with impression of myxœdema or nephrotic facies". The skin was dusky, jaundice was suspected but not definite. The thyroid gland was not enlarged. The liver was not palpable but the spleen was enlarged. There was no ascites.

The patient was anæmic (Hb 9·9 g. per 100 ml.) and the blood-urea was 158 mg. per 100 ml. The serum-bilirubin was 10·7 mg. per 100 ml., serum-alkaline-phosphatase 6·5 K.-A. units per 100 ml., thymol turbidity 1 unit, thymol flocculation 0, prothrombin index 1·5.

Later on the day of admission the patient had two more hæmatemeses and became drowsy. A transfusion of whole blood was begun. Next day she was still drowsy and jaundice was now obvious. She had further hæmatemeses and the transfusion was continued. She was also given chlortetracycline orally (500 mg. six-hourly). Despite repeated transfusion her Hb fell from 69% on admission to 27% five days later, and she died on the sixth day having been comatose for twenty-four hours.

Postmortem Findings

The liver weighed 720 g., and the cut surface showed deeply jaundiced areas of surviving liver tissue embedded in a deep red stroma. Microscopically there was widespread massive necrosis of liver parenchyma, and in many areas the liver cell had disappeared altogether leaving only stromal elements. There was some increase of periportal connective tissue, which was patchily infiltrated with plasma and lymphoid cells and

in which proliferation of bile-ducts was discernible. The thyroid gland was small and fibrous. Histologically it consisted of fibro-fatty tissue in which were small islands of thyroid tissue surrounded by dense accumulations of plasma cells and lymphocytes. The thyroid tissue showed recent acute necrosis, and no colloid containing alveoli were seen.

In each of these three cases, in which chronic thyroiditis and diffuse hepatic fibrosis were associated, the patient was a postmenopausal woman.

In the first a subtotal thyroidectomy had been carried out, on account of Hashimoto's disease, four years before her death from liver failure; this patient had had jaundice when she was 8 years old. In the second there had been clinical evidence of myxœdema for at least ten years before death from liver failure. In the third chronic thyroiditis was found incidentally at postmortem examination following death due to hæmorrhage from œsophageal varices and liver failure.

The striking feature of the histological examinations of the thyroids and livers from these patients was the similarity between the changes in the two organs: in both organs there were loss of the normal pattern, fibrosis, and collections of lymphocytes and plasma cells. In one case (case 3) there was acute necrosis in both the thyroid and the liver.

Discussion

Cases of coexisting thyroiditis and cirrhosis have been reported before. Thus Luxton and Cooke (1956) described two cases of diffuse hepatic fibrosis with clinical evidence of Hashimoto's disease, and Roitt and Doniach (1958) mentioned four cases of chronic thyroiditis with unspecified liver diseases; in one of these liver biopsy showed periportal lymphoid infiltration and fibrosis. The finding by Goudie et al. (1959) that the sera of elderly women with cirrhosis contain anti-thyroid antibodies significantly more often than the sera of patients with other diseases, and reports that the sera of some patients (about 8% [Doniach et al. 1959]) with Hashimoto's disease absorb complement in the presence of liver and other organs (Roitt and Doniach 1958, Anderson et al. 1959a and b), have also been taken to indicate an association between cirrhosis and thyroiditis. In our patients the histological appearances in the thyroid glands and the liver were strikingly similar including, in one case, the presence of necrosis in both organs.

The histological features we have described in the thyroid glands are similar to those reported in patients with chronic thyroiditis in whom anti-thyroid antibodies have been demonstrated (*Lancet* 1958, 1959, *Scot. med. J.* 1959, Smart 1959); indeed in one of our patients such antibodies were shown. The histological appearances in the livers, resembling as they do those in the thyroids, suggest to us a similar basis. There is in fact evidence that antibodies reacting with liver are present in the serum of some patients with diffuse hepatic fibrosis (Gajdusek 1958, Mackay and Gajdusek 1958).

A relationship between thyroiditis and diffuse hepatic fibrosis might be no more than a particular example of associations that have been postulated to exist between a number of disorders in which autoimmune mechanisms may be implicated (see Doniach et al. 1959). The thyroid gland is not always sectioned in cases where the patient has died of liver failure, but it would be clearly worth while to obtain more information on the histology of the thyroid in such patients. A study of the association between chronic thyroiditis and diffuse hepatic fibrosis might well throw further light on the ætiology of both. Whether autoimmunity initiates the disease in both organs, or whether it develops as the result of a disorder affecting both organs more or less simultaneously, cannot be said. Finally there remains the possibility that disease in one organ is the consequence of disease in the other; if that were so our clinical evidence suggests that the thyroiditis precedes the hepatic fibrosis.

Summary

Three postmenopausal women who died of liver failure all had chronic thyroiditis; in two of them this was the original presenting feature, but in the third it was found incidentally. The histological findings in the liver and thyroid glands were similar, consisting in disappearance of the normal pattern, fibrosis, and infiltration with lymphocytes and plasma cells.

An association between chronic thyroiditis and diffuse hepatic fibrosis is therefore suggested. If such could be established it might be regarded as another example of association between diseases in which autoimmune processes are involved.

We wish to thank Dr. W. Phillips and Dr. I. G. Jones for permission to publish these cases; Prof. H. Scarborough, Prof. J. Gough, Dr. Paul Fourman, and Dr. H. J. Whiteley for helpful advice; and Mr. M. H. Travers for the photographs.

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FAMILIAL GLOMERULONEPHRITIS AND AMINOACIDURIA

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MANY examples of familial nephritis have been reported (Mitchell 1930, Rinkoff et al. 1939, Tudor 1943, Perkoff et al. 1951, 1958, Sohar 1956, Sturtz and Burke 1956, Goldbloom et al. 1957). Osman (1927) stated that in 11% of all cases of nephritis there was a family history of renal disease. Familial nephrosis has been described by Vernier et al. (1957), and familial renal sclerosis by Clark (1951).

We describe here an example of familial glomerulonephritis associated with a metabolic renal abnormality.

Affected Family

In a family of 8 (fig. 1) 3 children (cases 1–3) died as a result of chronic glomerulonephritis; a 4th child died in infancy, the cause being unknown.

Case 1.—In December, 1954, when 12 years old, Barbara, although symptom-free, was found to have proteinuria and mild hypertension; " chronic nephritis with a good reserve of renal function " was diagnosed. In May, 1956, when her brother developed renal disease, she was more fully investigated. A blood-pressure of 135/90 mm. Hg was the only

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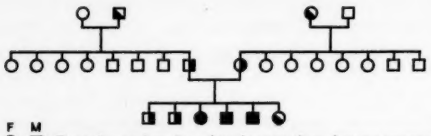
F M
Females and males: data incomplete, but no gross renal disease.
Aminoaciduria.
Died from other causes.
Died from glomerulonephritis.

Fig. 1—Family tree.

abnormal finding on clinical examination. Urinalysis revealed proteinuria, with a few red blood-cells and granular casts; hæmoglobin 16·3 g. per 100 ml., erythrocyte-sedimentation rate (E.S.R.) 13 mm. in the first hour (Westergren); blood-urea 26 mg. per 100 ml., serum-cholesterol 300 mg. per 100 ml.; serum-proteins 6·6 g. (albumin 4·2 g., globulin 2·4 g.) per 100 ml. Serum electrophoresis showed an increase in α_2-globulin. Urinary aminoacid chromatography showed pronounced generalised aminoaciduria, identical with that in other members of this family, and excretion of the nephrosis peptide. Chronic nephrotic nephritis was diagnosed, but treatment with cortisone did not control the proteinuria.

In July, 1956, an adequate percutaneous renal biopsy showed a possible slight increase in the thickness of the basement membranes of the glomerular capillaries. There was an area of interstitial fibrosis incorporating a single hyalinised glomerulus, and containing groups of lymphocytes. The convoluted tubules sometimes contained hyaline casts or red blood-cells. Chronic pyelonephritis was diagnosed.

The patient was treated with various antibiotics; none affected the course of the disease, and the proteinuria and mild hypertension persisted. The child remained symptom-free until January, 1958, when she complained of severe headaches and drowsiness. On admission to hospital in March, 1958, she was comatose and anuric, her blood-pressure was 260/160 mm. Hg, and there was gross cardiac enlargement. She died in cardiac failure shortly after admission.

Necropsy

Important findings included left ventricular hypertrophy and dilatation in keeping with hypertensive heart-failure, and terminal bronchopneumonia. The kidneys were three-quarters of the normal size, and each had a granular pitted surface with subcapsular petechial hæmorrhages (fig. 2). Histologically the outstanding feature was severe glomerular damage. In some glomeruli cellular proliferation within the capillary tuft was associated with thickening of the basement membrane, and in a few there was fibrinoid necrosis of individual capillary loops (fig. 3). Many well-formed epithelial crescents were present (fig. 4). More chronic changes included adhesions between the capillary tuft and the parietal layer of Bowman's capsule (fig. 5), and fibrosis of the tuft. There was moderate arteriolosclerosis. The tubules were atrophic, and some contained hyaline casts occasionally associated with polymorphonuclear leucocytes. There was much diffuse interstitial fibrosis and lymphocytic infiltration (fig. 6). The appearances

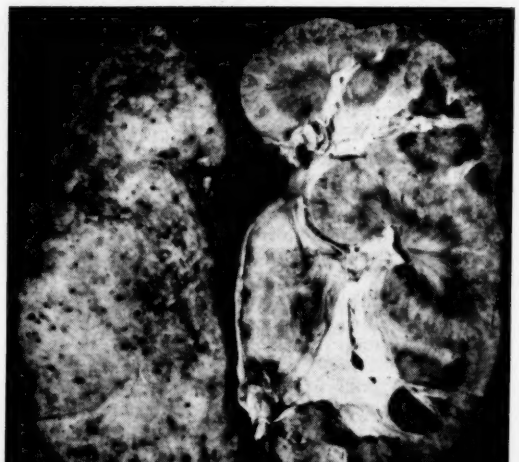

Fig. 2—Case 1: kidneys (×½).

were those of chronic glomerulonephritis, and the capillary necroses suggested an acute terminal phase.

Case 2.—Bernard was admitted to hospital in July, 1953, when 7 years old, complaining of abdominal pain, vomiting, and drowsiness for two weeks. Œdema and ascites were present. There was slight cardiac enlargement, and the blood-pressure was 180/140 mm. Hg. Urinalysis revealed gross proteinuria with occasional red blood-cells and hyaline casts. The hæmo-

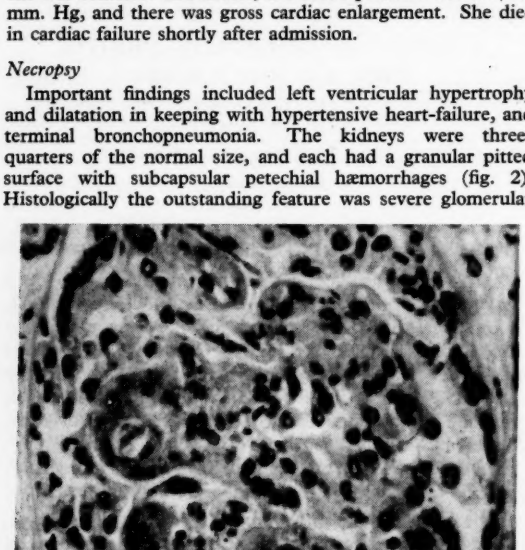

Fig. 3—Case 1: glomerulus, showing fibrinoid necrosis of several capillary loops (×340).

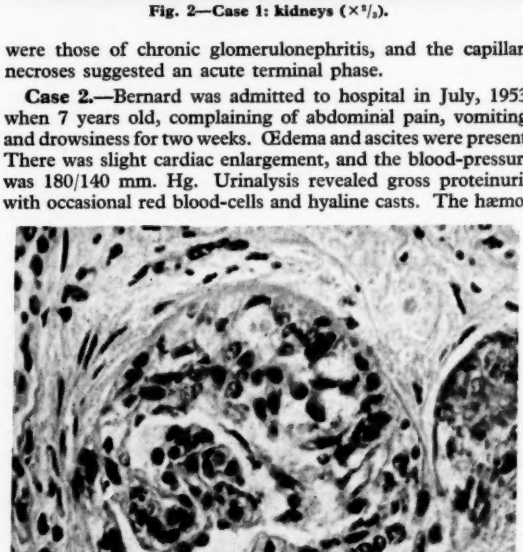

Fig. 4—Case 1: glomerulus with epithelial crescent (×300).

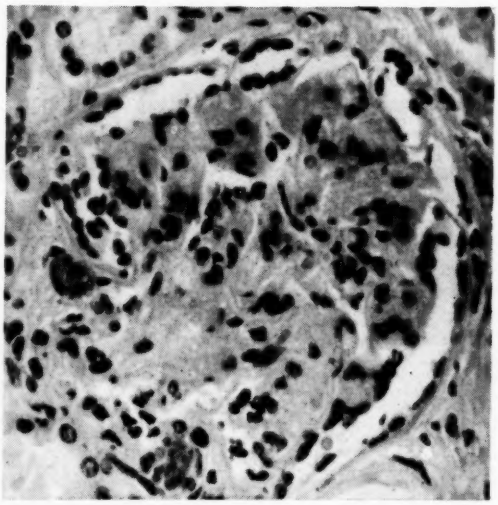

Fig. 5—Case 1: ischæmic fibrotic glomerulus with adhesions between the capillary tuft and the parietal layer of Bowman's capsule (×340).

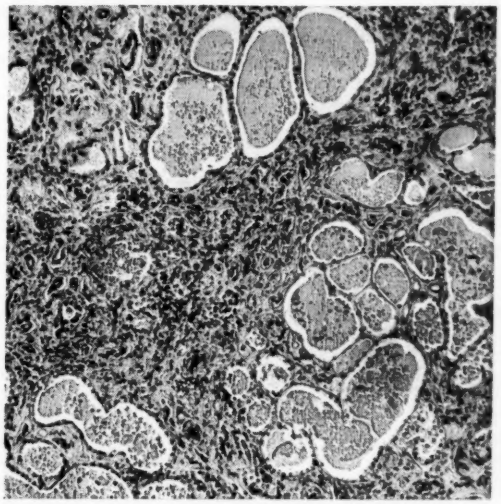

Fig. 6—Case 1: low-power view showing extensive interstitial fibrosis of cortex (×110).

globin was 15·5 g. per 100 ml., E.S.R. 43 mm. in the first hour, blood-urea 112 mg. per 100 ml., serum-cholesterol 476 mg. per 100 ml., serum-proteins 6·5 g. (albumin 3·5 g., globulin 2·5 g.) per 100 ml. The urea-clearance was 11% of the average normal. Subacute glomerulonephritis was diagnosed.

Treatment with low-protein and salt-free diet was ineffective, and renal failure progressed rapidly. This was associated with increasing hypertension which could not be controlled by hypotensive drugs; the patient died in cardiac failure. Permission for necropsy was refused.

Case 3.—Brian was first seen in May, 1956, when he attended hospital at the age of 7 years complaining of deafness. This was a conduction deafness which had followed tracheobronchitis two weeks previously, and it rapidly improved. Auditory-nerve function was normal. At this time proteinuria was discovered, and on further questioning a history of frequency of micturition and occasional enuresis following the influenzal illness was obtained. Clinical examination was unremarkable. His blood-pressure was 110/70 mm. Hg, and there was no œdema. Urinalysis confirmed the proteinuria, and revealed occasional red blood-cells and granular casts. His hæmoglobin was 15·5 g. per 100 ml., E.S.R. 14 mm. in the first hour, blood-urea 48 mg. per 100 ml., serum-cholesterol 330 mg. per 100 ml., serum-proteins 4·25 g. (albumin 2·5 g., globulin 1·7 g.) per 100 ml. Test of urinary specific gravity range showed a maximum specific gravity of 1020 and a minimum of 1000. Intravenous pyelography showed good concentration of the dye by both kidneys, outlining normal calyces and ureters. Serum electrophoresis showed an increase in α_2-globulin, and the only abnormal finding on urinary aminoacid chromatography was the presence of the nephrosis peptide. On these findings chronic nephritis was diagnosed.

BIOCHEMICAL FINDINGS IN AFFECTED FAMILY

—	1956	1958		Outcome
	Urinary chromatogram	Urinary chromatogram	Serum-alkaline-phosphatase (K.-A. units per 100 ml.)	
Father	G.A.	Normal	18	..
Mother	G.A.	G.A.	16	..
Allan	G.A.; N.	G.A.	26	..
Andrew	G.A.; N.	G.A.	18	..
Barbara (case 1) ..	G.A.; N.	..	..	Died 1958
Bernard (case 2) ..	..	..	..	,, 1953
Brian (case 3) ..	N.	..	..	,, 1957
Catherine.. ..	..	..	..	,, in infancy

G.A. = gross aminoaciduria. N. = nephrosis peptide.

Treatment with cortisone for six weeks did not alter the persistent proteinuria. The patient remained symptom-free till January, 1957, when he complained of severe headache. At this time he had much facial œdema, and the blood-pressure was 190/160 mm. Hg; but there were no other abnormal physical signs. The proteinuria was gross, hæmoglobin 10·3 g. per 100 ml., E.S.R. 58 mm. in the first hour, blood-urea 89 mg. per 100 ml., serum-proteins 4·35 g. (albumin 2·5 g., globulin 1·85 g.) per 100 ml. Hypotensive drugs failed to prevent a further rapid rise in the blood-pressure, and the patient died in congestive cardiac failure.

Necropsy

The finding of left ventricular hypertrophy and dilatation was in keeping with hypertensive heart-failure as the cause of death. The kidneys were reduced to about two-thirds of the usual size and presented a similar appearance throughout. The capsule was difficult to strip and left a granular surface with occasional subcapsular petechial hæmorrhages. The cortex was much reduced in width. Histologically there was considerable destruction of kidney tissue with much interstitial fibrosis and some scattered aggregations of lymphocytes. All the glomeruli showed some change. In many the tufts were completely or partially fibrosed; in others there were adhesions to Bowman's capsule; and a few epithelial crescents were seen. The tubules were reduced in number and were atrophied. Moderate arteriolosclerosis was found. Chronic glomerulonephritis was diagnosed.

Other Members of the Family

Clinical examination of the 2 surviving children and the parents was normal. Urinalysis and the estimates of renal function were within normal limits. Abnormal findings were raised serum-alkaline-phosphatase levels, which varied from 16 King-Armstrong units in the mother to 26 King-Armstrong units in the youngest child, and the urinary aminoacid chromatograms in which there was pronounced increase in the excretion of all the aminoacids (see table). In addition, the nephrosis peptide was detected in the urine of both children.

The parents are unrelated and are members of large families (fig. 1). It has not been possible to examine their siblings, but all are reported to be in good health and never to have had "kidney disease"; the surviving grandparents are healthy.

Discussion

In the present family 3 children died of diffuse glomerulonephritis, and the survivors, although appar-

ently healthy, have gross generalised aminoaciduria. This association, which has not to our knowledge been previously recorded, may be an ætiological factor in the present cases of glomerulonephritis.

In cases 1 and 3 the diagnosis of glomerulonephritis was confirmed at necropsy. The renal biopsy taken eight months before death in case 1 was in keeping with a diagnosis of chronic pyelonephritis. A comparison of this biopsy with necropsy material suggests that the specimen was from an unrepresentative area, or that the glomerular changes were in an early phase. The deafness in case 3 was related to the upper respiratory infection, and differs from that described by others in association with familial renal disease (Sohar 1956, Sturtz and Burke 1956, Perkoff et al. 1958).

The pattern of the aminoaciduria is identical in all the survivors and has remained constant, except in the father, throughout the observation period of two years. Aminoaciduria may occur in liver disease, but there is no conclusive evidence of this in any member of the present family. It may also be due to inherited or acquired abnormalities of the renal tubules (Dent 1954), and it is presumably of renal origin in this family. Lathem et al. (1955) stated that glomerulonephritis does not cause any abnormality of aminoacid excretion, but aminoaciduria occurs in children with nephrosis (Squire 1953, Woolf and Giles 1956, Hooft and Herpol 1959). That the pattern of abnormal aminoacid excretion is identical in the survivors would accord better with a congenital than with an acquired condition. The occurrence in two generations also suggests that it is an inherited defect, and has a genetic basis as have other syndromes associated with aminoaciduria (Harris 1957).

Earlier workers (Thomson and MacAuley 1920, Hurst 1923) referred to a *locus minoris resistentiæ* in the kidneys in familial nephritis. More recently Perkoff et al. (1958) suggested that renal disease in many members of a large kindred was related to "a local renal metabolic abnormality of an, as yet, unidentified nature". We believe that the aminoaciduria demonstrated in the present family may be a manifestation of such an intrinsic weakness. It is recognised that some inherited defects of aminoacid excretion are associated with characteristic morphological features—e.g., the "swan neck" lesion in Lignac-Fanconi disease (Darmady and Stranack 1957). We did not attempt kidney microdissection in the present series, but the presence of a renal structural defect is one way in which this organ's resistance to disease might be altered.

It may be useful to divide familial nephritis into two groups: (1) that associated with recognisable hereditary abnormalities (Hawkins and Smith 1950, Sturtz and Burke 1956, Goldbloom et al. 1957, present series); and (2) that attributed at present solely to epidemics of the nephrotoxic streptococcus (Tudor 1943). The latter group is indistinguishable from epidemic glomerulonephritis as described by Stetson et al. (1955) and many others. If genetically determined defects responsible for an increased tendency to glomerulonephritis in the latter group can be identified, prophylactic chemotherapy in these families might be expected to reduce the incidence of the disease by preventing streptococcal infection.

In addition to this family one other instance of familial renal disease has come to our notice. In the second family 2 of 3 children have died from pyelonephritis; the diagnosis was confirmed at necropsy in 1. We did not find any abnormality of aminoacid excretion in the surviving child or in the parents.

Summary

The occurrence of glomerulonephritis in 3 siblings is described. The surviving members of the family all have abnormal aminoaciduria. It is suggested that in this family an inherited defect responsible for the aminoaciduria also predisposes to glomerulonephritis.

It is important that families with a tendency to renal disease should be recognised, and investigations of apparently unaffected members undertaken to exclude any renal defect.

We are grateful to Prof. F. M. B. Allen and to Prof. J. H. Biggart for advice and encouragement during the preparation of this paper.

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PAROMOMYCIN IN THE TREATMENT OF SHIGELLA AND SALMONELLA INFECTIONS IN CHILDREN

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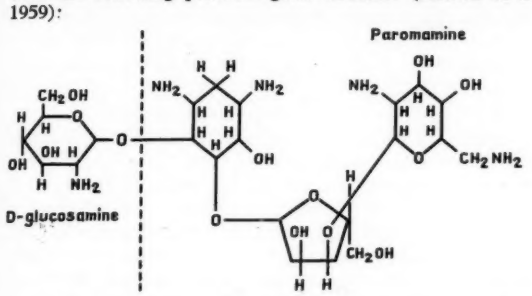
SEVERAL antibacterial drugs can control or shorten dysentery due to organisms of the shigella group. Complete eradication of the infecting organism from the bowel is much more difficult. In salmonella infections, persistent excretion of the infecting organism for six weeks or longer is relatively common. In our hospital, irrespective of treatment, the average period required for clearance of *Salmonella typhimurium* in a recent series of children was twenty-seven days.

For some time past we have been studying the effect of various drugs, singly and in combination, in cases and carriers of shigella and salmonella infections, particularly with regard to cure of the carrier state. We report here the results obtained with a new antibiotic, paromomycin.

Method

Paromomycin is an antibiotic derived from a strain of streptomyces. Chemically, it is a glycoside of D-glucosamine,

with the following probable gross structure (Haskell et al. 1959):



It is a white, water-soluble powder possessing bacteriostatic activity against various gram-negative organisms, including those of the shigella and salmonella groups. For our purposes, paromomycin was supplied as 'Humatin' in a form suitable only for oral administration, by which route it is considered by the manufacturers to be free from significant toxicity in laboratory animals.

The clinical trial was carried out entirely in the gastro-enteritis wards of our hospital. The following patients were included: 9 children aged 1–14 years with dysentery due to *Shigella sonnei*; 18 children aged 1–16 years with symptomless infection by *Sh. sonnei*; 8 children aged 7–16½ years in the convalescent stages of infection by *S. paratyphi B*; 2 children aged 10 months to 8 years with symptomless infection by *S. typhimurium*. All these infections were proved bacteriologically by examinations of stools or fæcal swabs before treatment.

Bacteriological diagnosis was made by culturing the fæcal material on desoxycholate citrate agar with and without overnight enrichment in selenite F or tetrathionate broth. Starting forty-eight hours after the last dose of drug, daily fæcal swabs or stools from each case were sent without delay to the laboratory. A case was regarded as clear of infection when four consecutive negative results were obtained. Specimens giving no bacterial growth on culture were disregarded, in order to exclude the antibacterial effect of residual drug in the fæces. During and after treatment, the specimens from each case were examined directly and by culture to detect staphylococcal or fungal superinfection.

TABLE I—EFFECT OF PAROMOMYCIN ON BACTERIA IN VITRO

Organism	No. of strains	Minimum inhibitory concentration (μg. per ml.)	
		Bacteriostatic	Bactericidal
S. typhi	1	5	20 (incomplete)
S. paratyphi B	4	5–10	10–20
S. typhimurium	3	10–20	20–50 (incomplete)
Sh. sonnei	12	20	50 (incomplete)
Staph. aureus (Oxford) ..	1	5	10 (incomplete)

Sensitivity tests were performed with each strain of the infecting organisms from these patients. As a routine, these were carried out by the disc-plate technique, the organism being assayed on blood-agar against blotting-paper discs impregnated with 20 μg. of paromomycin base. A number of assays were also carried out in broth.

Treatment

All the children in the trial were nursed in bed, with barrier precautions, until clear of infection. Children with severe diarrhœa were given half-strength Hartmann's solution by mouth for the first twenty-four hours, milk and water for the next twenty-four hours, and then a light diet. The paratyphoid cases were given a high calorie, low-residue diet. Symptomless cases received normal diet.

Paromomycin was normally given by mouth in a syrup containing 1 g. paromomycin in 4 ml. (1 drachm). In a few instances it was given as a powder, in milk, or in 150 mg. capsules. Daily dosage, in all cases, was 40 mg. paromomycin base per lb. (80 mg. per kg.) body-weight. No other antibacterial drugs were given along with paromomycin.

Results

Sensitivity in Vitro

An organism was regarded as sensitive when there was a clear zone, without growth, of at least 4 mm. around the margin of the disc. By this criterion, all the strains of *Sh. sonnei* and salmonellæ isolated from our patients were sensitive to paromomycin. Tests in liquid media (table I) showed that the action of paromomycin was mainly bacteriostatic; an incomplete bactericidal effect was obtained in concentrations of 20 μg. per ml. against some organisms.

Sonne Infection

9 children admitted with acute dysentery were treated with paromomycin; in each case the signs of infection subsided within two or three days, and 8 of the children were cured by a five-day course of treatment (table II).

18 symptomless carriers were also treated. Each of these children had received other drugs, or combinations of drugs, before admission, but their stools had remained positive for *Sh. sonnei*. 15 were cleared of the infection after a five-day course of paromomycin; 2 were cleared after a second course; 1 child remained infected but produced negative stools after a further course of neomycin (table II).

TABLE II—TREATMENT WITH PAROMOMYCIN OF SONNE INFECTION IN CHILDREN

Type of case	No. treated	Cured*	Not cured	Cured with another drug
Dysentery	9	8	1	1
Symptomless carriers..	18	17	1	1
Totals ..	27	25	2	2

* i.e., with four consecutive negative stools

As a background to the present study, the results of treatment of cases and carriers of Sonne infection with other drugs in 1958 and 1959 were analysed (table III). As these cases were treated before we started the paromomycin trial statistical comparison would be invalid; but the results suggest that paromomycin was, to say the least, not less active than some other drugs commonly used. 14 cases in this series remained positive after treatment; of these, all but 3 were clear of infection after further treatment (table III). The 2 children whose stools remained positive after paromomycin produced negative stools after neomycin was given.

Salmonella Infection

10 convalescent carriers were treated with paromomycin. 8 of these children had paratyphoid-B infection; 2 had *S. typhimurium* infection.

The paratyphoid cases, when diagnosed, had all been treated in the febrile stage with chloramphenicol. Of 12 thus treated, 8 continued to produce positive stools, and these 8 children were treated with paromomycin (table IV).

TABLE III—TREATMENT OF SONNE INFECTION IN CHILDREN WITH VARIOUS DRUGS (1958 AND 1959)

Drug	No. treated	Cured*	Not cured	Cured with another drug
Streptomycin with sulphonamide†	56	46	10	8
Neomycin‡	5	4	1	1
Other drugs	6	3	3	2
Totals ..	67	53	14	11

* i.e., with four consecutive negative stools.
† Dosage 67 mg. per lb. body-weight daily.
‡ Dosage 25 mg. per lb. body-weight daily.

TABLE IV—TREATMENT WITH PAROMOMYCIN OF CONVALESCENT CARRIERS (CHILDREN) OF SALMONELLÆ

Infection	No. treated	Cured*	Not cured	Cured with another drug
S. paratyphi B ..	8	5	3	0
S. typhimurium ..	2	1	1	1
Totals ..	10	6	4	1

* i.e., with four consecutive negative stools.

4 were cleared of infection after one course of paromomycin; 1 was cured by a second course. 3 cases remained positive.

Of the 2 children infected with *S. typhimurium*, 1 gave negative stools after a single course of paromomycin.

In each of the relapsing cases, the sensitivity of the reisolated organisms was retested against paromomycin. No change was detected in the two strains of *Sh. sonnei* or in the one strain of *S. typhimurium* thus tested. Of the four strains of *S. paratyphi B* reisolated in relapse, two showed partial growth in the inhibitory zone around paromomycin discs on solid media. On subculture, colonies from these zones were resistant to 20 μg. paromomycin per ml. in liquid media, whereas the parent strains were sensitive to 5–10 μg. per ml. This change affected only some of the bacteria in the reisolated strains, for assays of randomly selected colonies outside the inhibitory zones of the discs showed that many were still inhibited by the original levels of paromomycin.

SIDE-REACTIONS

In powder form, paromomycin was distasteful but caused no upset. As a syrup, it provoked mild nausea in a few older children. None had nausea or vomiting.

No other adverse reactions to the drug were noted. In 12 children tested, hæmoglobin levels and leucocyte-counts were essentially unchanged after courses of paromomycin. No abnormal changes were noted in routine samples of urine.

The stools passed during the period of treatment with paromomycin were often soft and colourless, indicating some overall suppression of the fæcal flora. There was, however, no evidence of serious mycotic or staphylococcal superinfection in these cases (table V). 1 child had a mild attack of diarrhœa with numerous *Candida albicans* in the fæces; a 2nd had overgrowth of candida in the stools, without symptoms.

TABLE V—OCCURRENCE OF *Staph. aureus* AND *Candida albicans* IN THE STOOLS OF CHILDREN TREATED WITH PAROMOMYCIN

Original infection	No. examined	No. of children with	
		Staph. aureus	*C. albicans*
Sh. sonnei	27	..	2
S. paratyphi B ..	8	..	..
S. typhimurium ..	2	..	..

Discussion

The infections included in this study are to a large extent self-limiting, and spontaneous clearance of the infecting organisms can occur at any time. Thus any antibacterial drug must be evaluated cautiously, especially when its use is confined to acute cases. The present trial included some children in whom the chronic carrier state, refractory to other forms of treatment, was well established. The eradication of infection in these cases is clearly a more reliable indicator of specific activity by the drug.

With these reservations, paromomycin appeared to eradicate *Sh. sonnei* in a high proportion of cases and carriers. In this respect it compares well with other forms of treatment in that, in our series, clearance occurred in 25 out of 27 cases in eight to twenty-four days and was as effective in chronic carriers as in acute cases.

In the smaller series of children with salmonella infection, paromomycin was less effective. In a larger series of salmonella infection the results obtained by McMath and Hussain (1959) were promising, especially when paromomycin was combined with streptomycin. We are, therefore, inclined to support their view that paromomycin warrants a more extensive trial in this type of infection.

Paromomycin proved active in vitro against various gram-negative organisms, including coliform commensals as well as pathogens. This range of activity resulted in some overall suppression of the coliform fæcal flora in our patients, who passed soft, relatively odourless stools, often two or three times daily, during treatment. No serious complications arose from this overall suppressive effect, nor was there during the trial any evidence of gastrointestinal irritation or systemic toxicity due to the drug.

The action of paromomycin in vitro seems to be mainly bacteriostatic against *Sh. sonnei* and *S. typhi*, though some organisms were lysed. A greater bactericidal action is exerted against some strains of *S. paratyphi B* at 20 μg. per ml., but this is evidently not complete enough to prevent the emergence of some resistance in vivo.

No drug has been found which will consistently eliminate these species of shigella and salmonella from persistent excretors (*Lancet* 1959). In this light, the results obtained with paromomycin seem to us promising.

Summary

Paromomycin, in a daily dosage of 40 mg. per lb. (80 mg. per kg.) body-weight was used in the treatment of shigella and salmonella infections.

In 8 out of 9 cases, and in 17 out of 18 carriers, of Sonne infection stools were bacteriologically negative after short courses of paromomycin. 5 out of 10 excretors of salmonella, similarly treated, had negative stools.

No serious toxic reactions or superinfections developed. Two reisolated strains of *S. paratyphi B* showed partial drug resistance.

Grateful acknowledgment is made to the nursing and technical staff who assisted in the work of this trial; and to Dr. H. W. Pearson and his staff of Messrs. Parke, Davis & Co., Ltd., for supplying paromomycin ('Humatin') together with helpful information about it.

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"... It is through chronic illness that one understands why the family has been defined as an autocracy ruled by its sickest member ... Inevitable human emotions, fear, perplexity, anger, shame, and guilt are experienced not only by the patient but by the members of his family. It is important that the physician have some basic understanding of the psychology of chronic illness, of prolonged convalescence and disability so that his mind can be freed so far as possible from enslaving emotions in order that he can deal clearly and intelligently with the emotional problems of those whom he is attempting to help."—Prof. JOHN ROMANO, *J. chron. Dis.* 1955, **1**, 695.

ASSESSMENT OF URINARY PHOSPHATE EXCRETION

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CHANGES in parathyroid activity are known to modify the renal handling of phosphate, and this mechanism is presumed to account for the low serum-phosphate of hyperparathyroidism and the high serum-phosphate of hypoparathyroidism. The assessment of the degree of phosphaturia in any given patient therefore not only is of physiological interest but may be of diagnostic value (Brush et al. 1955). There is not as yet any general agreement on the best procedure for making this assessment.

The inorganic phosphate of the blood-plasma is believed to be wholly filtrable through the glomerular membrane and then partially reabsorbed by the renal tubular epithelium (Smith 1951). The phosphate appearing in the urine is generally considered to represent that proportion of the filtered phosphate which has not been reabsorbed.

It is known from phosphate infusion studies in animals (Pitts and Alexander 1944) and in man (Anderson 1955) that in acute experiments the absolute amount of phosphate reabsorbed by the tubules rises with the filtered load until at high plasma levels the tubular maximum is reached, after which further increases in plasma level and therefore in filtered load are quantitatively reflected in the urinary excretion. Hence, without a change in renal function, the renal clearance of phosphate should vary with the level of serum-phosphate. But this normal relationship between serum and urine phosphate levels will be altered by any change in the renal tubular handling of phosphate. It is such a specific change in the renal handling of phosphate which is believed to account for the abnormal levels of plasma-phosphate in parathyroid disorders.

The proportion of filtered phosphate which is not reabsorbed is represented by the ratio of the phosphate clearance to the glomerular filtration-rate, and an approximate value for the latter can be obtained from the endogenous-creatinine clearance. The resultant phosphate/creatinine clearance ratio (Cp/Ccr) has already been widely used in the assessment of parathyroid activity with varying success but in a manner which generally fails to take into account the normal fluctuations in this ratio which follow fluctuations in plasma-phosphate level (Milne et al. 1952, Nordin and Fraser 1956). The present paper re-defines the simple procedure for the measurement of this ratio which we have reported before (Nordin and Fraser 1954), describes a method of correcting the ratio to take into account the plasma level of phosphate, and reports the results obtained in various clinical conditions.

Methods

Fresh samples of urine were obtained from all the subjects together with a venous blood sample taken at about the middle of the urine collection, which was usually a two-hour period. The test is preferably performed in the fasting state, and after some days on a normal or low phosphorus intake. Catheterisation was not employed because as we have pointed out previously (Nordin and Fraser 1954) the Cp/Ccr can be calculated from the concentrations of phosphate and creatinine in the plasma and urine without considering the volume, as follows:

$$\text{Cp/Ccr} = \frac{\text{Urine-phosphate} \times \text{plasma-creatinine}}{\text{Plasma-phosphate} \times \text{urine-creatinine}}$$

Inorganic phosphate and creatinine were measured in the plasma and urine by the methods of King and Wootton (1956).

Patients Studied

All the relevant cases seen in the years 1935–57 are included. The normal data were obtained from 53 members of the staff and patients convalescing from acute illnesses.

The 9 cases of primary hyperparathyroidism were all confirmed by operation.

The 17 cases of osteomalacia were inpatients with steatorrhœa, radiological thinning of the bones, and a serum calcium × phosphate product (in mg. per 100 ml.) of 25 or less. The great majority were confirmed by iliac-crest biopsy.

The 11 patients with hypoparathyroidism consisted of 9 postoperative cases, 1 idiopathic case, and 1 associated with steatorrhœa. Some of them were taking vitamin D.

The 48 cases of osteoporosis were of the type commonly called postmenopausal or senile which Nordin (1960) has defined as primary osteoporosis.

Results

Normal Subjects and Calculation of Normal Cp/Ccr

The normal relationship of plasma-phosphate to the Cp/Ccr was derived from the infusion data of previous workers as assembled and presented by Milne et al. (1952). By calculation, the regression equation of Cp/Ccr on plasma-phosphate was found to be *:

$$\text{Cp/Ccr} = 0{\cdot}055 \times \text{serum-P} - 0{\cdot}07 \text{ (standard error of Cp/Ccr} = 0{\cdot}06).$$

* This is a more accurate recalculation of our earlier formula (Nordin and Fraser 1956) for this line: Cp/Ccr = 0·05 plasma-P − 0·05 (S.E. = 0·06). The phosphate excretion index calculated by the earlier formula is almost identical with that derived from the more correct formula in this paper.

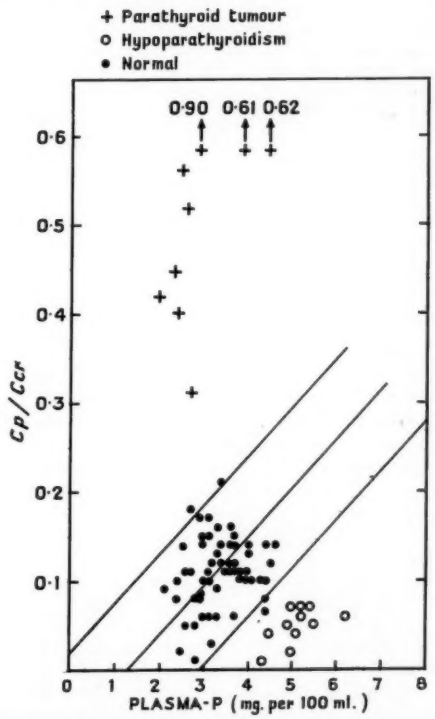

Fig. 1—Plasma-phosphate concentration and phosphate/creatinine clearance ratio in normal subjects and in patients with hyperparathyroidism and hypoparathyroidism.

The slope of the regression line is calculated from the data of Milne et al. (1952), but the limits are calculated from our normal subjects.

For the purpose of this calculation, and with the approval of Dr. Milne, it was assumed that the data up to a plasma-phosphate of 8 mg. per 100 ml. fell along a straight line.

The Cp/Ccr values from 53 normal subjects are shown in fig. 1 in relation to this regression line previously calculated from Milne's data. Their variance from this line has been calculated, and the range of 2 standard deviations was found to be $\pm 0{\cdot}09$. So the estimate and variance of the normal relationship between Cp/Ccr and serum-P becomes:

Cp/Ccr = 0·055 plasma-P − 0·07 (for normal Cp/Ccr values the range of 2 standard deviations from this estimate = $\pm 0{\cdot}09$).

Fig. 1 also shows the results obtained in 9 cases of primary hyperparathyroidism and 11 cases of hypoparathyroidism. It will be seen that in the cases of hypoparathyroidism the Cp/Ccr was abnormally low in relation to the plasma-phosphate level, and that in the cases of parathyroid tumour the Cp/Ccr was above the normal range for the plasma-phosphate.

Calculation of Phosphate Excretion Index (P.E.I.)

By applying the above regression-line equation to the plasma-phosphate level in any given case, it is possible to predict what the mean Cp/Ccr should be in normal circumstances, and so to measure the extent to which the observed Cp/Ccr differs from the predicted one. A difference of less than $\pm 0{\cdot}09$ denotes a point falling within our normal limits; larger differences represent points falling outside these lines. It is therefore possible to represent the extent to which any given observation departs from the predicted mean by a single value which we have called the phosphate excretion index (P.E.I.), and the results obtained in various metabolic disorders are shown in this way (fig. 2). As well as the 9 cases of parathyroid tumour, 16 out of 17 cases of osteomalacia had P.E.I. values of more than $+0{\cdot}09$. In addition, high values were observed in 4 out of 48 cases of osteoporosis (2 of them diabetics); 6 out of 16 cases of renal stone; 3 out of 6 patients with Cushing's syndrome or on steroids; 7 out of 7 cases of malignant disease with bone secondaries; and 7 out of 11 cases of uræmia. Low values are found in all 11 cases of hypoparathyroidism and 2 out of 17 cases of thyrotoxicosis.

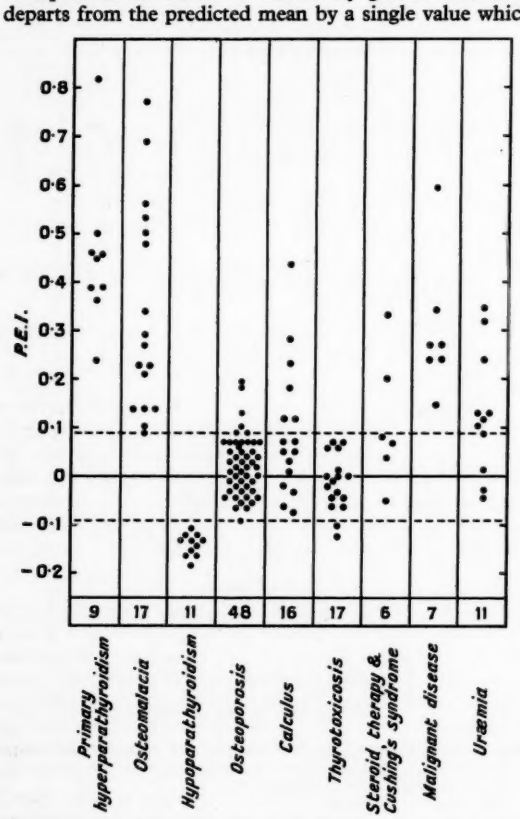

Fig. 2—Phosphate excretion index in various clinical disorders.

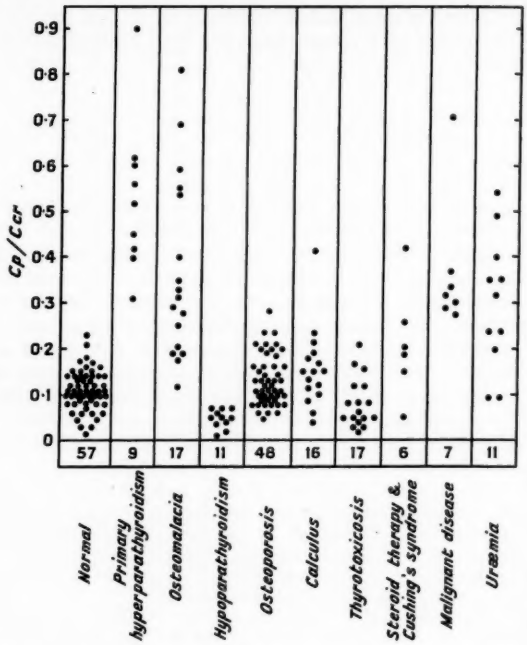

Fig. 3—The phosphate/creatinine clearance ratio in the normal subjects and in the cases shown in fig. 2.

Alternative Indices of Phosphaturia

Simple Cp/Ccr.—Fig. 3 shows the actual values of Cp/Ccr in the same cases without the application of any correction for plasma-phosphate level. It demonstrates that the "normal" range of Cp/Ccr extends from about 0·02 to 0·22, and that it is quite impossible to separate the different diagnostic categories from one another on this calculation alone. In particular, it is impossible to separate cases of hypoparathyroidism and osteomalacia from the normal subjects.

Urinary phosphate/creatinine ratio (P/Cr).—Milne (1951) has shown that there is a correlation between plasma-phosphate and urine-phosphate output in mg. per hour in normal subjects, but we have found that inaccuracies in bladder emptying make this relationship of little diagnostic value unless the samples are obtained by catheter. In normal subjects, however, an equivalent relationship exists between the plasma-phosphate level and the ratio of phosphate to creatinine in the urine, and fig. 4 shows the data on the same cases plotted in this way. The regression of the urinary phosphate/creatinine ratio (P/Cr) on the serum-phosphate has been calculated as follows:

$$P/Cr = 0{\cdot}145 \times \text{serum-phosphate} - 0{\cdot}12.$$

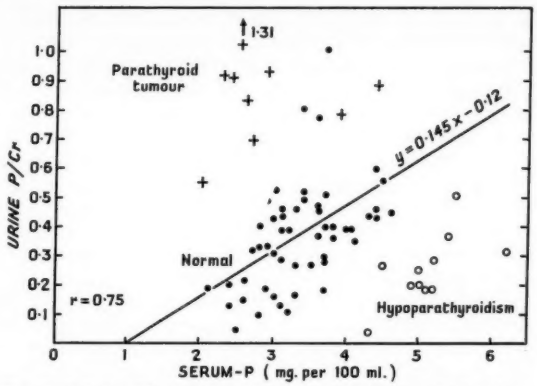

Fig. 4—Relationship between plasma concentration of phosphate and ratio of phosphate to creatinine in urine in normal subjects and in hyperparathyroidism and hypoparathyroidism.

The coefficient of correlation is 0·75. All 11 cases of hypoparathyroidism fall below and to the right of the normal data, and 7 out of 9 cases of parathyroid tumour above and to the left: the other 2 were uræmic.

P.E.I. with assumed plasma-creatinine of 1 mg. per 100 ml.—The existence of a relationship between urinary P/Cr and plasma-phosphate suggests that the estimation of plasma-creatinine might not be essential to the calculation of Cp/Ccr, and that in the absence of renal failure an arbitrary figure could be substituted for what is at best an unsatisfactory estimation. Fig. 5 therefore shows the P.E.I. on all the cases represented in figs. 2–4 (except those with uræmia) calculated with an assumed plasma-creatinine of 1·0 mg. per 100 ml. Comparison with fig. 2 shows that the separation of the cases of hyperparathyroidism from the normal range is less satisfactory by this calculation and that more cases of osteoporosis appear to have hyperphosphaturia.

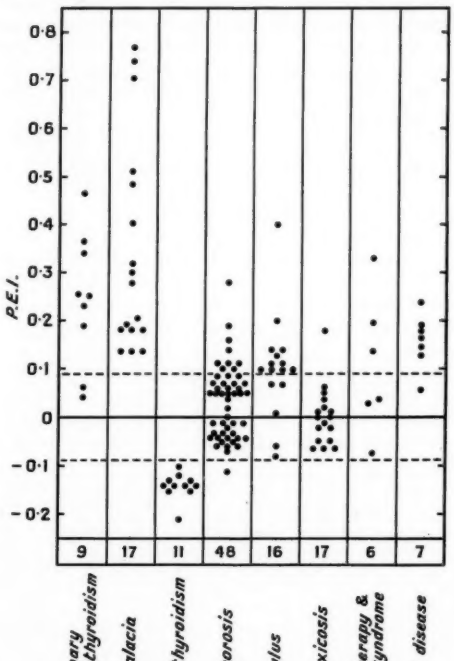

Fig. 5—Phosphate excretion index calculated with an assumed plasma-creatinine concentration of 1·0 mg. per 100 ml.

"*Reabsorbed-phosphate*" *index.*—Yet another method of assessing urine phosphate excretion has been suggested by Thomas et al. (1958) and by Morgan (1959). If the inferred tubular reabsorption of phosphate (1-Cp/Ccr) is multiplied by the plasma-phosphate a figure is obtained which represents approximately the amount of P reabsorbed per 100 mg. glomerular filtrate. If this calculation is applied to our data the results shown in fig. 6 are obtained. The absolute normal range is 1·8–4·0 mg. P reabsorbed per 100 ml. of filtrate. The separation of the cases of osteomalacia from the normal subjects is less satisfactory than by the P.E.I. procedure (fig. 2) but the most striking difference is that most cases of uræmia yield results in the normal range.

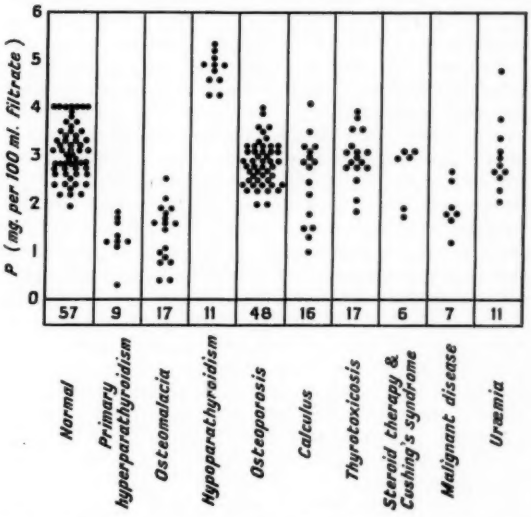

Fig. 6—Mg. of phosphate reabsorbed per 100 ml. of glomerular filtrate in various clinical disorders.

Routine Use of the P.E.I.

The results obtained in 350 consecutive observations of P.E.I. on 103 patients are shown in the accompanying table. 164 of these observations (on 55 patients) fell within the normal range. 186 on 48 patients were either high or low. The most striking feature of these observations is the high values found in patients taking large supplements of calcium glycerophosphate.

Discussion

We have shown that when the plasma P and the Cp/Ccr are considered in relation to one another, cases of primary hyperparathyroidism have a high clearance ratio and cases of hypoparathyroidism a low clearance ratio in relation to the concentration of plasma-phosphate. High clearances with low values for plasma-phosphate are also found in osteomalacia, presumably owing to the secondary hyperparathyroidism which is known to occur in this condition. This accords with our earlier data (Nordin and Fraser 1956) which have recently been confirmed by Talpers and Stein (1959).

ANALYSIS OF 350 CONSECUTIVE P.E.I. OBSERVATIONS

—	Total no. of observations	Total no. of cases	High values	Low values
Hypoparathyroidism on various doses of calciferol	122	4	30	46
Osteomalacia	61	5	57	0
Steatorrhœa (without osteomalacia)	13	3	1	2
Osteoporosis	34	34	4	0
,, on P supplements	85	36	39	0
Parathyroid tumour	2	2	2	0
Patients on steroids	10	1	1	0
Uræmia	5	1	1	0
Renal calculus	6	6	2	0
Thyrotoxicosis	3	3	0	0
Cushing's syndrome	1	1	1	0
Normal	8	7	0	0

For convenience in making this comparison in relation to plasma-phosphate, we have suggested the calculation of the phosphate excretion index which measures departures from the normal relationship and separates hyperparathyroid, euparathyroid, and hypoparathyroid cases from each other. We have not yet come across any false negatives (i.e., normal values in primary hyperparathyroidism) with this procedure, but we are aware that they occasionally occur (McGeown 1957, G. H. Morgan, personal communication). As far as false positives are concerned, it is clear that high values are usually seen in osteomalacia and frequently in uræmia, but this we attribute to the secondary hyperparathyroidism which is known to occur in these conditions (Nordin 1958). We have also seen high values in some cases of renal calculus without raised plasma-calcium but with hypercalcuria: these are examples of the syndrome of idiopathic hypercalcuria (Henneman et al. 1958) and may in fact represent a form of hyperparathyroidism or tubular disease, but we have also seen many normal values with hypercalcuria. High values are also seen in some cases of malignant disease with hypercalcæmia in which other workers have already reported a low rate of tubular reabsorption of phosphate (Thomas et al. 1958): these latter cases are therefore biochemically indistinguishable from primary hyperparathyroidism. Abnormally high values for P.E.I. may also be found in patients with Cushing's syndrome or on steroid therapy, in accordance with other evidence that the steroids reduce the renal tubular reabsorption of phosphate (Anderson 1959). Possibly this could be secondary to the rise in the filtered load of glucose which may occur in states of adrenocortical overactivity, since there is considerable evidence that phosphate and glucose compete for the same tubular reabsorptive pathway (Huffman et al. 1958). This may also explain the high values seen for P.E.I. in 2 cases of osteoporosis with diabetes mellitus; the high values in 2 other cases of osteoporosis out of 48 measured are unexplained. Clearly, however, the parathyroid hormone is only one of several factors which may influence the excretion of phosphate—albeit one of the major factors.

Our data suggest that the measurement of the P.E.I. provides some information about the excretion of phosphate in any given case and indicates whether or not it can be regarded as normal, although we are aware that the Cp/Ccr on which it is based does not measure accurately the proportion of filtered phosphate that is reabsorbed. Our data also suggest that this index of phosphaturia is better than the available alternative indices.

Various other ways have been suggested of assessing the rate of phosphate excretion. Many workers assume that the creatinine clearance is identical with the glomerular filtration-rate and subtract the Cp/Ccr from 1 to yield the tubular reabsorption of phosphate (T.R.P.) which they express as a percentage (Chambers et al. 1956). We agree with Hills and Burr (1958) that there is no advantage in this procedure and that it introduces an assumption which is unjustified. Other workers (Kyle et al. 1958) have confined themselves to the measurement of an absolute phosphate clearance calculated from a timed sample of urine. The preliminary results with this procedure are good so far as they go, but we believe from experience that sufficient accuracy to make this a useful procedure can only be obtained by catheterisation and we consider this unjustified in this context.

Both these procedures suffer furthermore from the weakness that they do not take into account the prevailing level of phosphate in the plasma. As we have shown in fig. 3, relatively poor separation between the various degrees of parathyroid activity is achieved by measuring the Cp/Ccr alone, and the same must be true of the T.R.P. and the simple phosphate clearance.

Certain workers (Thomas et al. 1958) have suggested an alternative method of correction for the plasma-phosphate concentration. They multiply the plasma-phosphate concentration by the T.R.P. and express the results as mg. of P reabsorbed per 100 ml. of glomerular filtrate. As we have shown in fig. 6, this calculation separates the various groups in much the same way as our calculation except that a few cases of osteomalacia and more cases of uræmia fall into the "normal" range. In fact, normal or even "hypoparathyroid" values are obtained in most cases of uræmia with high levels of plasma-phosphate, whereas in such cases the P.E.I. is almost invariably raised. In view of the abundant evidence of secondary hyperparathyroidism in glomerular renal failure (Goldman and Bassett 1954, Nordin 1958) we believe that the P.E.I. calculation is probably sounder than the calculation of mg. P reabsorbed per 100 ml. of glomerular filtrate, although we agree that the latter is a simple and attractive procedure.

It must be emphasised that our normal standards are not applicable to subjects on very high intakes of phosphorus. The disproportionate rise in phosphate clearance in these circumstances has already been reported by Crawford et al. (1950) and Goldman and Bassett (1958) and is being studied by us at present. It is well seen in our cases of osteoporosis taking calcium-glycerophosphate supplements and may be due to stimulation of the parathyroid glands by a raised serum-phosphate concentration.

Summary

The normal relationship between the plasma-phosphate concentration and the phosphate/creatinine clearance ratio has been calculated from the phosphate infusion data of other workers.

A simple procedure is described for determining the phosphate/creatinine clearance ratio and for calculating the extent to which it departs from the predicted normal value in any particular case. We have called this deviation from the normal value the phosphate excretion index. The normal range of this index is $-0{\cdot}09$ to $+0{\cdot}09$.

The clearance ratios were found to be abnormally high in relation to the plasma concentration of phosphate in primary hyperparathyroidism and in osteomalacia but abnormally low in hypoparathyroidism.

Abnormally high values were found in certain other conditions, some of which may be biochemically indistinguishable from hyperparathyroidism.

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PLASMA-INSULIN ACTIVITY IN ACROMEGALY AND SPONTANEOUS HYPOGLYCÆMIA

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IN recent years various methods for assaying plasma-insulin activity have been used in the study of cases of spontaneous hypoglycæmia, acromegaly, diabetes, and other conditions in which abnormal levels might be expected. The results of these assays appear to have led clinicians to believe that in some conditions a knowledge of the level of plasma-insulin activity is of significance for diagnostic or therapeutic purposes. To assess the value of such assays from this point of view, I have used the rat-diaphragm method in cases of acromegaly and spontaneous hypoglycæmia. In both these conditions abnormal levels have been reported.

Materials and Methods

Plasma Specimens

Heparinised blood was drawn with the subject at rest after an overnight fast. Following the separation of the plasma within one hour of collection, its glucose content was determined and raised to approximately 300 mg. per 100 ml. by the addition of solid glucose. Such plasma was stored at −10°C and diluted, where necessary, by the addition of glucose-saline buffer (see below) immediately before assay.

Estimation of Plasma-insulin Activity

A standardised assay procedure was used throughout these experiments (Wright 1957). The mean *glucose-consumption rate* of a group (three to eight) of hemi-diaphragms from eight rats incubated individually in undiluted plasma (2 ml.) was compared with that of another incubated in Krebs-Ringer bicarbonate buffer (2 ml.) containing glucose in a concentration of approximately 300 mg. per 100 ml. (glucose-saline buffer). The difference between the mean glucose-consumption rates of these two groups of hemi-diaphragms is termed the *insulin effect* of the plasma. Usually the hemi-diaphragms incubated in these two media did not come from the same rats; they were not paired. In no case were both hemi-diaphragms from any one rat incubated in the same medium. In most experiments other hemi-diaphragms were incubated in glucose-saline buffer containing insulin in concentrations of 10, 100, and 1000 micro-units per ml.; when diluted plasma of normal and acromegalic subjects was studied the effects of insulin were not examined.

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The glucose-consumption rates and insulin effects are expressed as μg. glucose per 10 mg. dry weight of tissue per 90 min.; hemi-diaphragms were weighed in the dry state and incubated for 90 min.

The mean *insulin equivalent* of any group of plasma specimens was deduced from its mean insulin effect and the mean effects produced by the three standard concentrations of insulin in these experiments (table I); it has been shown (Vallance-Owen et al. 1954, Wright 1957) that there is a direct relationship between glucose-consumption rate and the cube-root of the insulin concentration in the incubation medium. The insulin equivalent deduced from the mean effects produced by groups of diluted plasma specimens is stated in terms of undiluted plasma, the necessary corrections having been made for the degree of dilution used.

Results

EFFECT OF INSULIN ON GLUCOSE UPTAKE

The insulin effects produced by the pure hormone in the three concentrations used in varying combinations in 54 experiments are shown in table I; they are not significantly different from the results previously reported (Wright 1957).

TABLE I—STIMULANT EFFECTS OF INSULIN ON GLUCOSE CONSUMPTION BY THE ISOLATED RAT-DIAPHRAGM

Insulin concentration (micro-units per ml.)	Experiments (no.)	Mean insulin effect * (μg. glucose per 10 mg. dry wt. per 90 min.) ±S.E.M.
10	19	39±12
100	26	145±8·0
1000	54	237±6·3

* Insulin effect in individual experiments = mean glucose uptake of hemi-diaphragms incubated in presence of insulin minus mean uptake of those incubated in its absence.

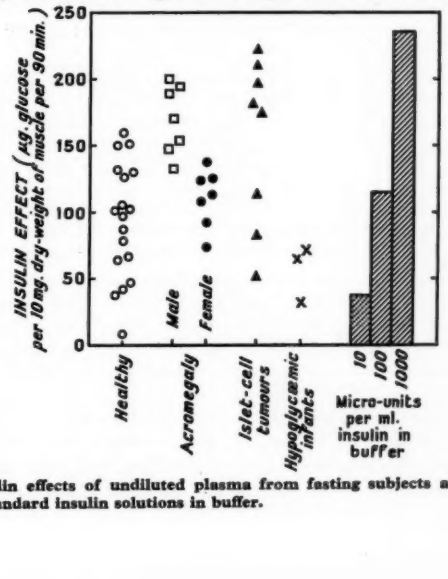
HUMAN PLASMA

The insulin effects of undiluted plasma samples from 43 persons are shown graphically in the accompanying figure.

Normal Subjects

The mean insulin effect of undiluted plasma from 18 fasted normal subjects (14 males and 4 females) was 94 (S.D. = 44). It is therefore unlikely (P = 0·95) that an individual specimen from a normal person would produce an effect greater than 182.

In 9 of these cases, all male, diluted plasma was assayed. In each experiment eight rats were used, four



Insulin effects of undiluted plasma from fasting subjects and of standard insulin solutions in buffer.

TABLE II—INSULIN EFFECTS OF UNDILUTED AND DILUTED PLASMA FROM FASTED NORMAL AND ACROMEGALIC SUBJECTS

Subjects	No.	Sex	Mean insulin effect *			Mean insulin equivalent †		
			P	P/4	P/16	P	P/4	P/16
Normal ..	9	M	100 (7)	90 (11)	34 (8)‡	74	200	..
Acromegalic	7	M	170 (10)	150 (9)	110 (13)	360	1000	1500
	7	F	111 (8)	104 (13)	60 (9)	104	360	310

* μg. glucose per 10 mg. dry wt. muscle per 90 min.; for undiluted plasma (P) and plasma diluted 1 : 4 (P/4) and 1 : 16 (P/16) in glucose-saline buffer. S.E.M. shown in parentheses.
† micro-units per ml.
‡ Only 4 specimens examined.

hemi-diaphragms from different animals being incubated individually in each plasma medium. In all 9 cases undiluted plasma and plasma diluted 4-fold in glucose-saline buffer were used as incubation media, but in only 4 was 16-fold diluted plasma employed. Table II shows that the mean *insulin effect* of plasma diluted 4-fold is not significantly different from that of undiluted plasma, whereas that of plasma diluted 16-fold is much smaller.

The mean *insulin equivalent* of the undiluted plasma is 74 micro-units per ml. Plasma assayed after 4-fold dilution has a mean insulin equivalent of 200 micro-units per ml. Little significance can be attached to the insulin equivalent deduced from the mean insulin effect produced by plasma diluted 16-fold, which was only weakly active. It seems unlikely, however, that the insulin equivalent is increased further when the degree of plasma dilution exceeds 1 : 4.

Acromegalics

Plasma samples were examined from 7 male and 7 female patients with typical clinical signs of acromegaly. All were normoglycæmic in the fasting state.

Abnormal plasma-insulin activity appears to be confined to the male patients. Thus, table II shows that the mean effect produced by undiluted plasma from male acromegalics is significantly greater ($P < 0.01$) than that of plasma from the females, which is not significantly different from that of the 9 normal males. No significant change in mean plasma-insulin effect was noted in either the male or the female acromegalics on 4-fold dilution of the plasma, though in both cases further dilution did result in a fall in mean insulin effect. The main difference between these two groups is that the mean insulin effect produced by plasma of male acromegalics is greater than that of females at all degrees of dilution.

The mean insulin equivalent of undiluted plasma from the male acromegalics (360 micro-units per ml.) is approximately 5 times that of plasma from normal subjects. Similarly the mean equivalents of plasma assayed after 4-fold (1000 micro-units per ml.) and 16-fold (1500 micro-units per ml.) dilution are at least 5 times the values observed in similarly diluted normal plasma. In female acromegalics the plasma insulin equivalents at all degrees of plasma dilution are not significantly different from those of normal plasma.

TABLE III—INSULIN EFFECTS OF UNDILUTED PLASMA FROM FASTED SUBJECTS WITH SUBSEQUENTLY PROVEN ISLET-CELL TUMOURS OF PANCREAS

Case no.	Age (yr.)	Sex	Duration of symptoms (yr.)	Plasma-sugar (mg. per 100 ml.)	Insulin effect (μg. glucose per 10 mg. dry wt. per 90 min.)	Insulin equivalent (micro-units per ml.)
1	45	F	10	33	84 (±7)	52
2	32	M	1	65	114 (±15)	118
3	43	M	1	28	119 (±22)	590
4	54	F	½	47	176 (±15)	420
5	52	M	1	39	223 (±49)	830
6	54	F	½	24	53 (±23)	14
7	31	M	2½	25	212 (±8)	730

S.E.M. shown in parentheses.

Islet-cell Tumours of the Pancreas

Plasma was examined in 7 cases from whom histologically proven islet-cell tumour tissue was subsequently removed. Blood was drawn after at least a 12-hr. fast, and in 6 cases the patient was hypoglycæmic at the time. Paired hemi-diaphragms from five rats were incubated in (*a*) undiluted plasma and (*b*) glucose-saline buffer; the mean insulin effects produced in each case are shown in table III. High insulin effects were observed in only three cases (nos. 3, 5, and 7), the remainder being within the normal range (see figure).

Idiopathic Hypoglycæmia of Infancy

Plasma was obtained from 3 young children who had had repeated spontaneous attacks of hypoglycæmia for which no cause could be found. At the time of blood collection all were hypoglycæmic (plasma-glucose concentration < 40 mg. per 100 ml.) and in 2 cases symptoms appeared soon afterwards. The insulin effects produced by these plasma specimens were essentially normal (see figure).

Discussion

Normal Subjects

The present results confirm previous observations that undiluted plasma from fasted normal subjects has a mean insulin effect equivalent to that of the pure hormone in a concentration of 50–100 micro-units per ml. (Vallance-Owen and Hurlock 1954, Wright 1957). This value is somewhat less than the range (50–350 micro-units per ml.) obtained more recently by Martin et al. (1958) who used the epididymal-fat-pad method of insulin assay.

Randle (1957a), using the isolated rat diaphragm, found that the insulin content of plasma assayed after 4-fold dilution was greater than that assayed in the undiluted form; in other words, plasma diluted 4-fold contains more insulin than one would expect following this degree of plasma dilution. Further dilution, however, decreased the insulin content in proportion to the degree of dilution used (Randle 1954c, 1957a). This paradoxical situation was also observed by Takeuchi et al. (1957), who used dog plasma, and is confirmed by the present results.

The insulin equivalent of plasma assayed after 4-fold dilution is of the order of 200 micro-units per ml., judging by the present results; higher levels are unlikely to be obtained if plasma is assayed in a more dilute form. Of those who have used diluted plasma or serum for assay in vitro Groen et al. (1952) and Takeuchi et al. (1957) have obtained results of this order. On the other hand, Randle (1954c, 1957a), Willebrands and Groen (1956), and Willebrands et al. (1958), who also used diluted plasma, suggest that normal plasma contains insulin in concentrations greater than 1 milli-unit per ml. These very high levels have not yet been adequately explained, and it seems unlikely that the effect produced by plasma dilution is entirely responsible.

Acromegalics

The plasma of acromegalic patients was examined with two objects in view. First it was thought that some relationship might exist between the plasma-insulin effect and the degree of functional activity of the pituitary tumour. Secondly, some confirmation of the very high levels of plasma-insulin activity reported by Randle

(1954a, 1955, 1957b) in acromegalic patients seemed desirable.

The injection of growth hormone into normal cats increases plasma-insulin activity (Randle and Young 1956), and the removal or irradiation of the pituitary tumours of acromegalic patients reduces their previously high levels of plasma-insulin activity (Randle 1954a, 1955). From these observations and the low level of activity found by Randle (1954b) in plasma from patients with hypopituitarism, it was inferred that high levels of plasma-insulin activity might be found only in those cases in which the pituitary tumour was in an active secretory state. On the basis of clinical observations and the results of various laboratory investigations (J. H. Briggs, W. J. H. Butterfield, P. H. Wright, unpublished) the 14 acromegalics (table II) were classified according to the degree of tumour activity thought to be present. Contrary to expectations, however, very active plasma was obtained from clinically inactive cases, and patients with active tumours yielded only weakly active plasma. It was, however, noted that male acromegalic patients, whose plasma-insulin activities were generally higher than those of the females, were also more resistant to the effects of intra-arterial insulin (Hardwick et al. 1959).

In no case were the plasma-insulin equivalents comparable with the high values (40–500 milli-units per ml.) reported by Randle (1954a, 1955) even when diluted plasma was used for assay. It seems probable, therefore, that, as in the case of normal plasma, some factor other than plasma dilution is responsible for the extremely high figures reported by Randle.

Islet-cell Tumours of the Pancreas

Although several groups of workers (Groen et al. 1952, Vallance-Owen et al. 1955, Kelly 1956, Willebrands and Groen 1956, Randle 1957a) have reported high levels of activity in plasma or serum obtained from such cases, this finding is not invariable. Willebrands and Groen (1956), who studied 11 proven cases, found abnormally high levels of activity in only 7. The present findings confirm that a normal level of activity may be found in subsequently proven cases of insulin-secreting tumours of the pancreas. Failure to demonstrate abnormal insulin activity in the plasma may be due to incorrect timing of the blood sample. Willebrands and Groen (1956), for example, have reported 2 cases in which samples were drawn on more than one occasion, and in both cases normal and high levels were recorded at different times. The finding of a single normal plasma-insulin level in no way contraindicates the diagnosis.

Idiopathic Hypoglycæmia of Infancy

Though a rare condition, spontaneous hypoglycæmia of infancy can cause permanent mental impairment if it is not recognised and adequately treated (McQuarrie 1954). In a large proportion of cases the underlying cause is not known, and the part played by endogenous insulin secretion has not been assessed. For this reason treatment in most cases has been empirical and has been directed towards abolishing the hypoglycæmic attacks responsible for the cerebral damage. Attempts have however been made in recent years to identify those cases which are due to increased insulin secretion by the pancreas or by an islet-cell tumour, and which would therefore benefit by surgical treatment.

Randle examined plasma from 3 of the cases described in detail by Cochrane et al. (1956), but in only 1 did he find high plasma-insulin activity. Laparotomy in this case revealed an abnormally large amount of islet-cell tissue made up predominantly of β-cells; partial pancreatectomy produced temporary relief. Both of the other cases had normal plasma-insulin levels though 1, which was submitted to laparotomy, showed hyperplastic changes in the pancreatic islet tissue. Vallance-Owen also examined plasma from a case described by Kinsbourne and Woolf (1959) and reported a normal level of activity; no laparotomy was performed. Of the cases examined here only 1 was submitted to laparotomy, and again hyperplastic changes were reported in the islet tissue. In all 3 cases, however, normal levels of plasma-insulin activity were found (see figure). It appears, therefore, that even in those cases where there is collateral evidence of increased β-cell activity in the pancreas, normal plasma-insulin levels may be found.

COMMENT

The results of the present experiments and a review of other published work show that for diagnostic and therapeutic purposes plasma-insulin assays are of little practical use in individual cases. On the other hand, in studies of groups of patients with the same clinical conditions they have provided useful information.

A small proportion of the patients who present with clinical signs of spontaneous hypoglycæmia are ultimately shown to have islet-cell tumours of the pancreas (Conn and Seltzer 1955). These cases can usually be identified by rigorously applying simple clinicopathological tests, such as those suggested by Whipple (1952). Knowledge of the plasma-insulin activity in suspected cases apparently provides no more reliable information than the results of these much simpler investigations. The results may, in fact, be misleading unless it is appreciated that a normal level of plasma-insulin activity does not contra-indicate the diagnosis. In other conditions, such as acromegaly, diabetes, spontaneous hypoglycæmia of infancy, hypopituitarism, and possibly others in which carbohydrate metabolism is deranged, the results of other and simpler investigations are of more significance to the clinician in individual cases than a knowledge of the plasma-insulin level.

On the other hand, the hypotheses put forward by Himsworth and Kerr (1939) and later by Lawrence (1951) to explain the existence of two contrasting clinical types of human diabetes were confirmed when their plasma-insulin levels were investigated; no insulin-like activity is detectable in the plasma of young ketotic diabetics who require insulin therapy for survival, while essentially normal levels are found in the plasma of the older obese group (Bornstein and Lawrence 1951, Vallance-Owen et al. 1955). Similar useful information has been obtained from studies of acromegalics and of animals treated with growth hormone.

The abnormal levels of plasma-insulin activity reported in acromegalic patients and in normal cats treated with growth hormone appear to be due to increased insulin secretion by the pancreas (Randle and Young 1956, Randle 1957b). If, as previously suggested (Wright 1957), the effect produced by undiluted plasma is due to the biologically effective circulating insulin and that of diluted plasma is a measure of the total insulin content, then the plasma of male acromegalics contains 5 times (360 micro-units per ml.) the concentration of biologically effective insulin and at least 5 times (1·0–1·5 milli-units per ml.) the total amount of insulin present in normal plasma; as in normal plasma, about two-thirds of the

circulating hormone is inactive. The substance which inactivates the circulating insulin in acromegalic patients may be similar to, if not identical with, the insulin inhibitor extracted from normal plasma by Vallance-Owen et al. (1958a and b); this substance is not present in the plasma of hypophysectomised patients, and its inhibitory action is disproportionately reduced by dilution. Thus the abnormal insulin effects produced by diluted plasma from male acromegalics could be due to the presence in undiluted plasma of large amounts of an insulin inhibitor whose effects are abolished by plasma dilution; no such inhibitor has yet been isolated or identified. The abnormal amount of insulin present in undiluted plasma may be necessary to compensate for the abnormal resistance of otherwise sensitive peripheral tissues. This hypothesis, though it may account for the high levels of activity observed in male subjects, does not explain why undiluted and diluted plasma from comparable female acromegalics have essentially normal levels of activity.

Randle (1956) has shown that the rat-diaphragm method of insulin assay is " sensitive but not very precise " —an assessment with which Willebrands and Groen (1956) agree. Concentrations of the order of 100 micro-units per ml. were easily detected in the present experiments, though in lower concentrations (10 micro-units per ml.) insulin did not always produce significant effects in individual experiments. The insulin equivalent values deduced from the effects produced by individual plasma specimens must be regarded as only approximate: the correct value may be anything from a half to twice the estimated figure. Thus, though this method of assay is very sensitive, its inaccuracy may be responsible for its failure to provide information of clinical significance in individual cases. There is considerable evidence (Groen et al. 1952, Randle 1954c, Vallance-Owen and Hurlock 1954, Randle and Taylor 1958) that the biological effects produced by plasma are due to the insulin which it contains, but other substances may also be present which augment or diminish its effects. Further investigations, similar to those of Field and Stetten (1956) and Vallance-Owen et al. (1958a and b) and aimed at the detection and identification of such inhibitors and augmentors in plasma, may yield more useful information concerning abnormal carbohydrate metabolism in human disease than the less specific plasma-insulin assays carried out in the past.

Summary

Insulin assays were carried out on plasma drawn from 18 normal subjects, 14 acromegalics, 7 patients with islet-cell tumours of the pancreas, and 3 children with idiopathic spontaneous hypoglycæmia.

Normal undiluted plasma has a biological effect equivalent to that of insulin in a concentration of approximately 70 micro-units per ml. The insulin equivalence of plasma diluted at least 4-fold is about 200 micro-units per ml.

Plasma from female acromegalics, assayed in the undiluted and diluted form, has essentially normal biological activity, while at all levels of dilution plasma from male acromegalics is significantly more active. It is suggested that the latter contains high concentrations of an insulin inhibitor.

Plasma from 3 of the cases of islet-cell tumours was abnormally active. It is concluded that normal levels of activity in suspected cases do not contraindicate this diagnosis.

Normal levels of activity were found in the 3 cases of spontaneous hypoglycæmia of infancy.

Whereas knowledge of plasma-insulin activity may help to explain the underlying causes of abnormal carbohydrate metabolism in some pathological conditions, assays in individual cases seldom provide information of use to the clinician.

I should like to thank those clinicians of other hospitals who kindly supplied me with plasma from the cases of spontaneous hypoglycæmia; Dr. P. M. Bishop, Prof. W. J. H. Butterfield, and Dr. J. H. Briggs for their cooperation in the study of acromegalic patients carried out in this hospital; Prof. R. H. S. Thompson for his encouragement and advice; and Mr. K. G. Kilbourn for his skilled technical assistance.

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LEUCINE AND PELLAGRA

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PELLAGRA has long been known to be predominantly a disease of maize-eaters. The association of pellagra with maize consumption has been attributed, among other factors, to the low tryptophan content of maize, and to the poor availability of its nicotinic acid. The disease is rare in areas where rice constitutes the staple. In nearly ten years' experience with many cases of nutritional deficiencies, we have seen only 4 classical cases of pellagra among the rice-eating population of Coonoor.

On the other hand, in Hyderabad, a city nearly five hundred miles further north, we frequently encounter cases of pellagra. Careful examinations of the dietaries of the poor segments of the population in Coonoor and Hyderabad failed to reveal any striking differences with regard to the intake of different nutrients; but, whereas rice is the sole staple in Coonoor, the dietaries of the poor segments of the population in Hyderabad invariably include the millet *Sorghum vulgare* (jowar). In practically every case of pellagra investigated by us in Hyderabad, a history of regular consumption of jowar with or without

AMINOACID COMPOSITION OF MAIZE, JOWAR, AND RICE

—	Tryptophan‡	Leucine‡	Isoleucine‡	Nicotinic acid§
Maize* ..	0·8	14·9	6·4	1·4
Jowar†	1·2	12·9	6·1	1·8
Rice†	1·2	8·0	6·0	1·2

* Baumgarten et al. (1946).
† Balasubramanian et al. (1952).
‡ g. per 100 g. protein.
§ mg. per 100 ml.

rice was obtained. In only 1 case was there a history of consumption of maize in addition to jowar and rice.

Comparison of the chemical composition of rice, jowar, and maize (see accompanying table) shows that the nicotinic-acid content of jowar is similar to that of rice. The reported tryptophan content of different strains of jowar varies widely, certain strains having nearly as high a content of the aminoacid as is found in rice while certain others have low values as in maize (Carpenter and Kodicek 1950). Both jowar and maize have, however, one common feature with regard to their aminoacid composition—namely, a high content of leucine. Elvehjem (1956) reported that the dietary supplementation of leucine at 1% level caused retardation of growth in rats subsisting on low-protein diets (9% casein), but that such growth retardation was not observed if the dietary protein intake was raised to 18%. The average daily protein intake in the dietaries of the pellagrins investigated here was of the order of 45 g. (9% protein), the protein being mainly derived from cereals including jowar. The possible role of aminoacid imbalance resulting from relative excess of leucine in the pathogenesis of pellagra

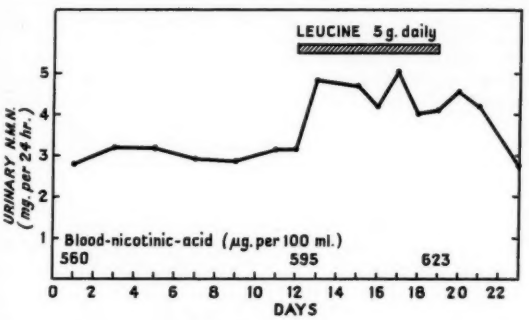

Fig. 1—Effect of supplementation with leucine on urinary N.M.N. excretion in a healthy subject.

was investigated, and the preliminary results are described here.

Experimental

Effect of Administration of Leucine on Urinary Excretion of N-methyl Nicotinamide (N.M.N.) in Healthy Volunteers and in Pellagrins

2 normal healthy male subjects were put on a basal diet providing roughly 10% protein, and their urinary N.M.N. excretion was determined daily by the method of Carpenter and Kodicek (1950). The basal diet was continued until a fairly stable level of N.M.N. excretion was attained. The volunteers were then given a daily supplement of 5 g. L-leucine along with one meal in a single dose, for seven days, and their urinary N.M.N. excretion was determined daily. Blood-nicotinic-acid levels were determined by the method of Sweeney and Hall (1951) (with some modifications) before, during, and after leucine supplementation.

Similar studies were also carried out in 3 patients with pellagra.

To determine whether the changes in urinary N.M.N. excretion brought about by leucine administration could be influenced by isoleucine, 2 other healthy male subjects were investigated. These subjects also received 5 g. leucine daily for three days after the initial stabilisation period, but for four days thereafter they received 2 g. of DL-isoleucine daily in addition to the 5 g. L-leucine.

To facilitate the quantitative interpretation of the changes in N.M.N. excretion in terms of nicotinic-acid metabolism, two healthy volunteers, who had been earlier investigated with leucine as above, received a 15 mg. oral dose of nicotinic acid and the increase in their urinary excretion of N.M.N. was determined.

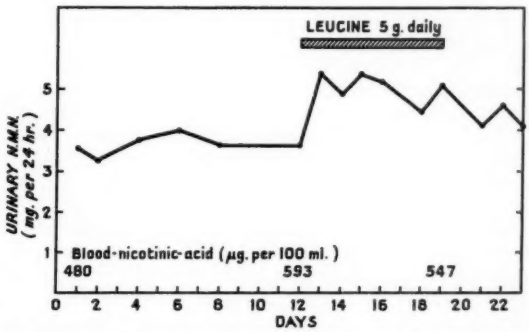

Fig. 2—Effect of leucine supplementation on urinary N.M.N. excretion in another healthy subject.

Effect of Isocaloric and Isonitrogenous Substitution of Rice by Jowar on Urinary N-methyl Nicotinamide Excretion

3 pellagrins were put on a basal diet providing 10% protein derived from rice and wheat, and the daily urinary N.M.N. excretion was determined. After the N.M.N. excretion had stabilised, rice in the diet was replaced by jowar and the daily urinary N.M.N. excretion on this diet was studied. Actual analysis of the two diets revealed that the rice-wheat diet in the 3 cases provided 7·3, 7·9, and 7·6 mg. nicotinic acid daily, while the jowar-wheat diet provided 7·8, 8·1, and 7·5 mg. nicotinic acid daily.

Effect of Administration of Large Amounts of Leucine in Pellagrins

2 patients with pellagra were placed on a basal diet supplying 45 g. of protein daily, the protein being mainly derived from jowar. After a preliminary stabilisation period these patients were given 10 g. L-leucine—twice daily in 1 case and thrice daily in the other—along with their principal meals. The urinary N.M.N. excretion was studied daily, and their clinical condition was carefully watched.

In this study the cases of pellagra were chronic, and the patients were not seriously ill. The patients volunteered for the investigation. We were confident that any deleterious effect of administering leucine could be corrected effectively and promptly by administration of nicotinic acid.

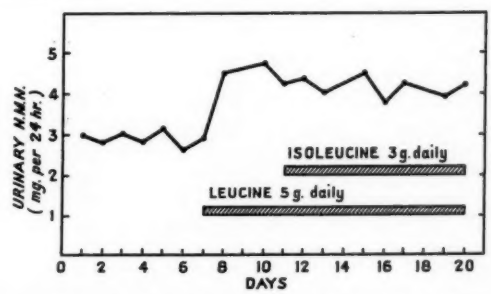

Fig. 3—Effect of simultaneous supplementation with leucine and isoleucine on urinary N.M.N. excretion.

Results

Effect of Administration of Leucine on Urinary Excretion of N.M.N.

The results of this study are illustrated in figs. 1–3. In all subjects investigated, both healthy volunteers and cases of pellagra, urinary excretion of N.M.N. increased immediately after administration of leucine. The rise in N.M.N. excretion brought about by 5 g. L-leucine daily represented an increase of nearly 50% over the basal level. Within a few days after the withdrawal of leucine, N.M.N. excretion returned to the basal level in all cases. There were no significant changes in the blood-nicotinic-acid levels. Determination of blood-nicotinic-acid levels in the same individual on a standard diet showed wide fluctuations, the values ranging from 660 μg. per 100 ml. to 1000 μg. per ml.

The increase in N.M.N. excretion brought about by leucine did not appear to be influenced by simultaneous administration of isoleucine (fig. 3). The administration of isoleucine did not alter the N.M.N. excretion pattern.

In the 2 healthy volunteers in whom the changes in N.M.N. excretion after administration of nicotinic acid were also studied, it was found that the administration of 15 mg. nicotinic acid resulted in an increase of urinary N.M.N. excretion of the order of 8·3 mg. and 7·5 mg. This suggests that the average increase of 1·7 mg. in N.M.N. excretion brought about by the administration of 5 g. of L-leucine reflects approximately an additional 3·5 mg. of nicotinic acid metabolised daily.

Effect of Isocaloric and Isonitrogenous Substitution of Rice by Jowar on Urinary N.M.N. Excretions

The effect of substituting jowar for rice in a typical case is illustrated in fig. 4. The replacement of rice by

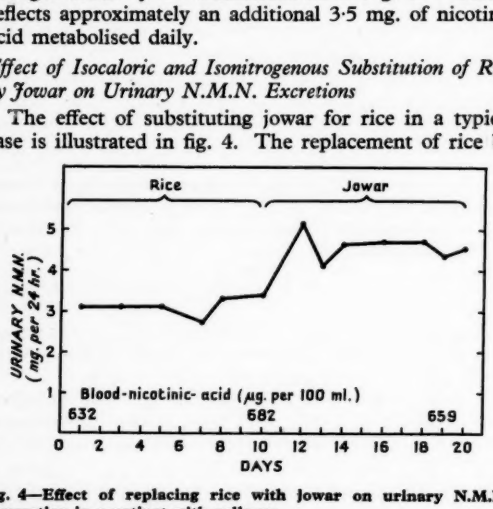

Fig. 4—Effect of replacing rice with jowar on urinary N.M.N. excretion in a patient with pellagra.

jowar resulted in a prompt increase in urinary N.M.N. excretion over the basal level observed in the "rice period". This increase was maintained as long as jowar was continued. After the withdrawal of jowar and the reinclusion of rice, N.M.N. excretion returned to the original low level.

It was calculated that the daily amount of leucine contained in the jowar diet was of the order of 5·3 g. The increase in N.M.N. excretion observed was also of the same order as that obtained with 5 g. L-leucine daily. Supplementation with isoleucine did not influence the N.M.N. excretion pattern on the jowar diet.

Effect of Administration of Large Amounts of Leucine in Pellagrins

In the course of the studies, 5 g. L-leucine daily was administered to 4 patients with pellagra for seven days. This was not associated with any appreciable effects on the clinical picture. The clinical features in 2 other cases in which larger amounts of leucine were given daily were as follows:

Case 1.—The patient was admitted with classical extensive skin changes, oral manifestation of vitamin-B-complex deficiency, and diarrhœa. On admission, apart from a feeling of anxiety, he did not seem to be mentally abnormal. He answered questions promptly and correctly. He continued in this state for four days, during which he was maintained on the basal diet to attain a stable level of N.M.N. excretion. On the fifth day he was given 30 g. of L-leucine in divided doses of 10 g. each at six-hourly intervals. Towards the end of this day the patient was found to behave in an agitated manner, to become incoherent in his talk, and to exhibit delusions of grandeur. The periods of excitement were found to alternate with short periods of severe depression. An additional dose of 10 g. of L-leucine was administered next morning, and by noon the patient became uncontrollable and violent. At this stage leucine was discontinued and he was given nicotinic acid intramuscularly. Within forty-eight hours after the initiation of nicotinic-acid therapy the patient's mental state had reverted to normal.

Case 2.—On admission the patient exhibited the classical skin changes and severe glossitis and had diarrhœa. He appeared alert and answered questions intelligently; he did not show mental changes. He was placed on the basal diet, and after the period of stabilisation he was given 20 g. L-leucine daily in divided doses of 10 g. each along with the principal meals. Leucine administration was continued for sixteen days and was then stopped.

Unlike all other cases of pellagra seen by us, in which some clinical improvement results from admission to hospital, even on the basal diet without nicotinic-acid supplementation this patient did not improve clinically; but there was no evidence of worsening of the skin condition or glossitis. Three days after leucine was started, the diarrhœa became more severe and the patient complained of insomnia. On the sixth day the patient became severely depressed and apprehensive; his answers to questions were no longer prompt. When leucine was stopped on the sixteenth day the patient seemed slightly disoriented. Three days after cessation of leucine administration, his mental condition became suddenly worse. He became violent with paranoid delusions and had to be forcibly restrained; his speech was incoherent. At this stage treatment with nicotinic acid was initiated and within forty-eight hours the mental condition returned to normal.

The urinary excretion of N.M.N. was followed throughout the period. Immediately after leucine administration was started there was an increase in N.M.N. excretion, which was maintained throughout the period of leucine supplementation. Three days after leucine was discontinued, when the patient's mental condition had worsened, N.M.N. excretion was still at the same high level as during the period of leucine administration. It was, however, noticed that the increase in the level of N.M.N. excretion brought about by the feeding of 20 g. L-leucine in this case was not significantly greater than the increase observed with 5 g. L-leucine in the healthy subjects and other cases of pellagra.

During the period of leucine administration, the patient lost nearly 2·5 kg. body-weight. Within three days after leucine was stopped the weight loss was arrested, and thereafter the patient started gaining weight.

Discussion

While pellagra has long been known to be associated with maize consumption, in the present study the disease has been found to be related to the consumption of the millet "jowar" (*Sorghum vulgare*). The increase in urinary N.M.N. excretion brought about by the replacement of rice by jowar suggests that the greater prevalence of pellagra in jowar-eaters than in rice-eaters may not be

attributable to deficiency in tryptophan or poor availability of its nicotinic acid. It has been shown in the present study that the administration of leucine brings about increased urinary N.M.N. excretion. This finding appears important since both maize and jowar have a high leucine content.

The precise significance of the increase in urinary N.M.N. excretion brought about by leucine requires elucidation. This increase is unlikely to be due to greater availability of nicotinic acid, because both maize and jowar, which are rich in leucine, have been associated with increased prevalence of pellagra. Apparently the aminoacid imbalance caused by relative excess of leucine in diets which are marginal with regard to protein may result in depletion of nicotinic acid from the tissues. The exact role of leucine in nicotinic-acid metabolism needs further investigation.

The increase in N.M.N. excretion brought about by supplementation with 5 g. of L-leucine daily would roughly correspond to the metabolism of an additional 3·5 mg. nicotinic acid daily. In diets which are already marginal with regard to nicotinic acid, this may be an important factor.

It would be premature to draw conclusions from these studies as to the role of leucine in the pathogenesis of pellagra. Case 2, in whom the effects of large doses of leucine was investigated, lost nearly 2·5 kg. body-weight in a fortnight during which leucine was administered. This possibly suggests that the increase in N.M.N. excretion brought about by leucine may not be a specific effect of leucine on nicotinic-acid metabolism, but reflects increased tissue catabolism due to the aminoacid imbalance. On the other hand of 6 subjects—2 healthy and 4 pellagrins—in whom the effect of leucine was investigated, only 2 with pellagra (including case 2) showed reduction in body-weight; in the remainder the increase in urinary N.M.N. excretion was associated with a stationary body-weight.

Summary

Oral administration of 5 g. L-leucine daily brought about an increase in urinary excretion of N-methyl nicotinamide excretion both in healthy subjects and in patients with pellagra. This increase was not influenced by isoleucine.

Isocaloric replacement of rice by jowar brought about an increase in the urinary N-methyl nicotinamide excretion in healthy subjects and in patients with pellagra. This increase also was uninfluenced by isoleucine.

Oral administration of 20–30 g. L-leucine daily to 2 patients with pellagra was associated with temporary deterioration of their mental condition, which was reversed when leucine was discontinued and nicotinic acid was administered.

We are grateful to Messrs. Hoffman La Roche, Basle, Switzerland, for their generous gift of leucine, used in this study; to Mr. S. N. Jagannathan for the blood-nicotinic-acid estimations and Mr. C. M. Manuel for technical assistance; and to the Director of Medical Services, Andhra Pradesh, and the medical officers of the Osmania General Hospital for their cooperation

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Preliminary Communication

SALICYLATE-INDUCED FALL IN PLASMA PROTEIN-BOUND IODINE IN HYPERTHYROIDISM

PREVIOUS work from this laboratory has demonstrated a pattern of metabolic changes produced in normal subjects by a large single dose of sodium salicylate by mouth.[1] This pattern was associated with a fall in plasma protein-bound iodine (P.B.I.) within two hours.[2] A fall in plasma-P.B.I. after long-continued administration of salicylate in therapeutic dosage has also been shown in rats and man.[2] Similar results were reported by Austen et al.[3]

The mechanism of these changes has been discussed elsewhere.[2 4] There is no evidence of a direct effect on the thyroid,[3] although the interference of salicylate with goitre-formation in thiouracil-treated rats indicates that it suppresses production of thyroid-stimulating hormone.[4] Analogy with the fall in P.B.I. after administration of dinitrophenol to rats [5] suggests that salicylate interferes with the normal feedback mechanism—possibly situated in the hypothalamus—which controls the circulating level of thyroid hormone.[6]

We have now studied the effect of salicylate on the raised level of plasma-P.B.I. in hyperthyroid patients.

METHODS

Observations were made on eight patients who had had no treatment beyond rest and sedation in hospital.

The diagnosis of hyperthyroidism was confirmed by the usual investigations—uptake of ^{131}I, basal metabolic rate, and plasma-P.B.I. After a preliminary period of 3–8 days, salicylate was administered orally as calcium acetylsalicylate in divided 4-hourly doses between 10 A.M. and 10 P.M. to a total of 6–8 grammes a day. Fasting blood-samples were taken daily before, during, and after the period of salicylate administration.

Plasma-P.B.I. was determined by a modification of the method of Acland.[7] The finding of Austen et al.[3] that salicylate does not interfere with determination of P.B.I. was confirmed by direct addition of salicylate to plasma and also by addition of salicylate at a level of 70 mg. per 100 ml. to the washed precipitate before ashing. The method described by Trinder [8] was used for the determination of the plasma-salicylate in the same samples.

Measurements of thyroid secretion-rate were carried out after therapeutic doses of ^{131}I in three other hyperthyroid patients, using the technique of Goldsmith et al.[9] The administration of carbimazole 30 mg. 8-hourly prevented the reabsorption of ^{131}I. Serial counts over the thyroid were made with a collimated scintillation detector and the counts were plotted on a semilogarithmic scale (fig. 2).

RESULTS

The effect of salicylate on the first hyperthyroid patient (A) is shown in fig. 1.

From an initial plasma-P.B.I. level of 14·0 μg. per 100 ml. there was a progressive fall to 10·6 μg. by the 4th day of salicylate administration (6 g. per day) when the plasma salicylate-level had reached 41 mg. per 100 ml. Withdrawal of the drug

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2. Charnock, J. S., Good, B. F., Hetzel, B. S. *Aust. J. exp. Biol. Med. Sci.* 1959, **37**, 473.
3. Austen, F. K., Rubini, M. E., Meroney, W. H., Wolff, J. *J. clin. Invest.* 1958, **37**, 1131.
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9. Goldsmith, R., Herbert, C., Lutsch, G. *J. clin. Endocrin. Metab.* 1958, **18**, 367.

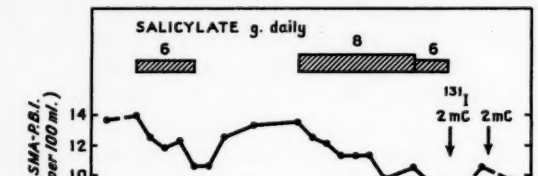

Fig. 1—Depression by salicylate of elevated plasma-P.B.I. in hyperthyroidism. The patient (A) is a woman of 50.

was associated with a rise of the plasma-P.B.I. to 12·6 μg. per 100 ml. after 2 days and to 13·4 μg. after 4 days and with rapid fall in the plasma-salicylate to zero. After 8 days salicylate was readministered in doses of 8 g. per day. The plasma-P.B.I. fell to 9·8 μg. per 100 ml. by the 6th day when the plasma salicylate reached 53 mg. per 100 ml. A fall to 9·0 μg. occurred by the 10th day, after which salicylate was discontinued and a dose of 2 millicuries of ^{131}I was given on the same day. The following day the plasma-P.B.I. was 8·6 μg. 4 days later the level had risen to 10·8 μg. and the plasma-salicylate had fallen to zero: later that day a further 2 millicuries of ^{131}I was given.

Similar falls have been noted in seven other hyperthyroid patients given salicylate in a dosage of 6 g. per day for 4 days.

The data from these patients are summarised in the table. The values indicate a mean fall in the plasma-P.B.I. from 13·8 μg. per 100 ml. to 11·5 μg. after one day and to 9·6 μg. after 4 days of salicylate administration by which time the mean plasma-salicylate had reached 29 mg. per 100 ml. Plasma-P.B.I. values on the 2nd and 3rd days of salicylate administration lay between those for the 1st and 4th days, confirming the progressive fall shown by patient A (fig. 1). Two days after withdrawal of salicylate the mean plasma-P.B.I. level had risen to 11·5 μg.

The effect of salicylate on thyroid secretion was studied in three other patients after therapeutic doses of ^{131}I, and fig. 2 shows the result in one of them.

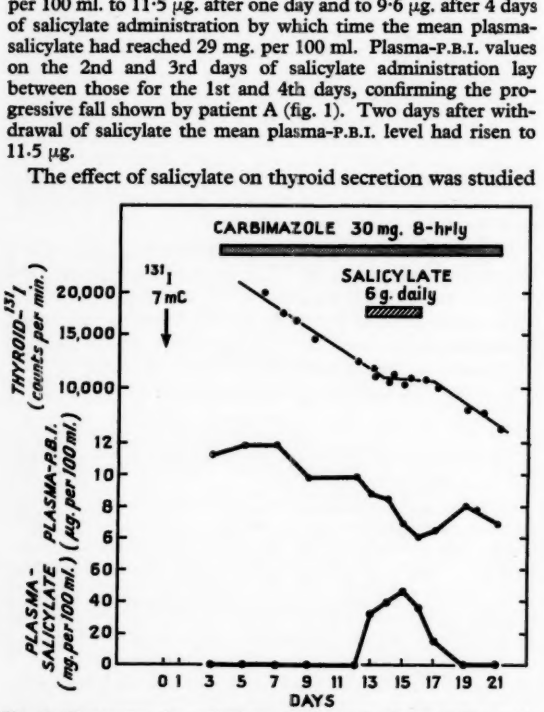

Fig. 2—Depression by salicylate of elevated plasma-P.B.I. and thyroid secretion in hyperthyroidism. The patient is a woman of 48.

During the preliminary period of carbimazole administration, the plasma-P.B.I. fell from 12·0 μg. per 100 ml. to 10 μg., and a further sharp fall to 6·2 μg. took place after the administration of salicylate. Within 48 hours of the administration of salicylate the rate of decay of thyroid ^{131}I slowed indicating a fall in thyroid secretion. After the withdrawal of salicylate, the rate of fall in thyroid ^{131}I increased and the plasma-P.B.I. rose to 8·2 μg. Similar results were obtained in the other two patients.

DISCUSSION

The data reveal that salicylates depress the high level of plasma-P.B.I. in hyperthyroid patients. In normal subjects such a fall in the circulating hormone level has been attributed to an interference with the feedback mechanism.[2 3 5] Comparison with a normal group indicates a similar proportional effect on the plasma-P.B.I. by salicylate.[10] These observations suggest that the feedback mechanism controlling the circulating thyroid hormone is as sensitive to salicylate in hyperthyroidism as it is in normal subjects.

The reduction of thyroid secretion caused by salicylate in three patients with hyperthyroidism resembles the reduction seen in normal subjects, as reported by Wolff and Austen.[4] Other studies have shown similar effects and time-relationships after the use of Lugol's solution in hyperthyroid patients.[9 11] These changes suggest some interference with thyroid-stimulating hormone activity—either a reduction in secretion, an inhibition of its effect on the thyroid, or both.[9 11] This could mean that, in hyperthyroidism, the thyroid is partly under the control of the pituitary. However, this does not accord with a recent report describing two cases in which hyperthyroidism persisted after hypophysectomy.[12]

EFFECT OF SALICYLATE ON PLASMA PROTEIN-BOUND IODINE IN HYPERTHYROIDISM

Subject	Age	Plasma-P.B.I. (μg. per 100 ml.)				Plasma salicylate (mg. per 100 ml.)†
		Before salicylate*	Period of salicylate administration		2 days after withdrawal of salicylate	
			1 day	4 days		
A	52	13·9	12·5	10·6	12·6	41·0
B	37	14·4	12·8	11·0	12·3	20·0
C	59	10·1	9·0	6·0	6·3	40·0
D	42	12·9	9·7	9·0	9·2	22·0
E	39	15·0	13·0	9·6	14·0	27·0
F	26	15·3	12·6	11·8	14·4	25·0
G	36	12·7	9·5	8·2	12·0	20·0
H	30	15·9	12·7	10·5	..	37·0
Mean	...	13·8	11·5	9·6	11·5	29·0

* Mean of two values during preliminary period of observation.
† After four days salicylate administration (6 g. per day).

The fall in plasma-P.B.I. appears to have preceded the effect on thyroid secretion. This may indicate the operation of an additional mechanism, particularly as there was a consistent, though significantly smaller, fall in plasma-P.B.I. after salicylate in six hypothyroid subjects maintained on desiccated thyroid when compared with a normal group.[10] A striking fall in plasma-P.B.I. has also been observed in thyroxine-maintained thyroidectomised rats given salicylate.[13] Until recently it has not been possible to demonstrate interference with protein-binding of thyroxine by salicylate in vitro, but Ingbar[14] has now

10. Hetzel, B. S., Good, B. F., Wellby, M. L., Charnock, J. S. Proceedings Fourth International Goitre Conference (to be published). 1960.
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shown that it can occur. Clearly more than one mechanism may be operating in this action of salicylate on plasma-P.B.I.

Our subsequent observations indicate that Lugol's solution causes a similar rapid fall in plasma-P.B.I. which takes place before the effect on thyroid secretion previously shown.[9 11] In fact, in three hyperthyroid patients given both drugs, the rate of fall in plasma-P.B.I. after salicylate closely resembled that seen after Lugol's solution. On the other hand, no effect on the sleeping pulse-rate has been noted with salicylate, whereas after Lugol's solution it consistently fell. This may be related to the metabolism-stimulating effect of salicylate,[1] still evident in hyperthyroidism. This limits the possible value of salicylate as therapy in hyperthyroidism. Further investigations with related drugs free from the hypermetabolic and other undesirable side-effects of salicylate are now being undertaken.

SUMMARY

In ten patients with hyperthyroidism, salicylate in doses of 6–8 g. per day consistently reduced the plasma protein-bound iodine. The action resembles that of Lugol's solution, but salicylates do not affect the sleeping pulse-rate.

We are indebted to the honorary physicians of the Royal Adelaide Hospital and the Queen Elizabeth Hospital for access to patients under their care. This investigation was supported by the National Health and Medical Research Council of Australia with whole-time grants to two of us (M. L. Wellby and J. S. Charnock).

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New Inventions

NEW, PULSE-GIVING, HYDRAULIC PUMP FOR EXTRACORPOREAL CIRCULATION

DESPITE the increasing number of publications on extracorporeal circulation no essential changes in the pumping principles have been described. All designs have been adapted from pumps previously used in industry (' Zigma ' pumps, roller pumps, plate pumps, and membrane pumps). In these pumps the blood is propelled and reflux prevented by means of a direct mechanical effect on the tube conveying the blood through the pump.

In order to avoid the disadvantages of such pumps, a pump was constructed which ensures a pulsatile blood-stream without significant destruction of the blood-corpuscles.

In essence the pump consists of a tube which is rhythmically compressed and expanded by hydraulic action, while valves inside both ends of the tube ensure that the blood passes through the tube in one direction only.

The pump chamber is shown diagrammatically in fig. 1. A wide plastic tube (1) is enclosed in a rigid chamber (2) completely filled with liquid (5). Valve boxes (3 and 4) are inserted, watertight, into each end of the chamber by means of interior connecting pieces on to which the plastic tube is fitted. By means of a motor-driven piston (6) in the bottom of the chamber the volume of the rigid chamber is rhythmically decreased and increased, resulting in equivalent compression and expansion of the plastic tube. The volume of blood which, in this way, is rhythmically pumped out of and into the tube will be exactly the same as the known volume change of the chamber caused by the movement of the piston, the valves

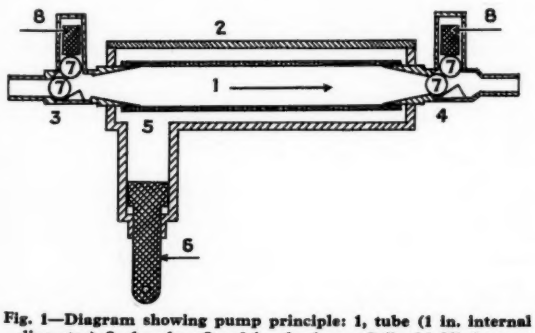

Fig. 1—Diagram showing pump principle: 1, tube (1 in. internal diameter); 2, chamber; 3 and 4, valve boxes; 5, liquid-filled space; 6, piston; 7, perspex balls; 8, weights keeping balls in position.

being constructed as direct-current, horizontal, pressure-loaded ball valves impeding any reflux. The motive force is supplied by a three-phase A.C. motor (0·5 H.P.) rotating with a constant maximum number of revolutions. By means of a special gear, both the stroke-volume and the frequency of strokes can be varied. The stroke-volume can be varied continuously from nil to 70 ml. per stroke; when the stroke-volume is increased the piston continues to start from " zero " position. The frequency can be changed continuously from 20 to 150 strokes per minute; and accordingly the total minute-volume can be varied from nil to about 10 litres. The stroke-volume, the frequency, and the minute-volume can be read on a single scale.

The valve boxes and the valve balls are made of ' Perspex '. The other parts of the pump which come into direct contact with the blood are plastic tubes.

The present pump was constructed for use in connection with any type of oxygenator. In this case a screen oxygenator

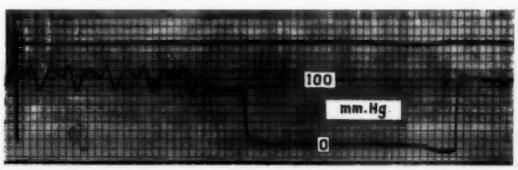

Fig. 2—Electrocardiogram and pressure-curve from femoral artery during perfusion under cardioplegy: registration by a condenser manometer through a 100 cm. Cournand heart catheter no. 8, introduced about 5 cm. above the inguinal ligament.

was used (Mark III, Gibbon type). Therefore, three pump chambers were applied with a reciprocal mechanical coupling of the pumps in the following way:

Pump no. 1 acts as an arterial pump. Pump no. 2 transports the blood from the venous reservoir to the top of the oxygenator. These two pumps are mechanically coupled and both transport exactly the same quantity of blood. By means of a single manipulation one of the two pumps can be stopped while the other pump continues to work independently. Pump no. 3 transports to the top of the oxygenator the 2 litres of blood per min. necessary to maintain the blood-film on the screens of the oxygenator. In order to avoid 2 litres of excess blood constantly passing through the oxygenator, pump no. 3 is mechanically connected with pump no. 2 in such a way that pump no. 3 transports only the supplementary amount necessary for the maintenance of the blood-film on the screens of the oxygenator; and pump no. 3 is automatically disconnected when pump no. 2 transports 2 litres of blood or more.

In constructing this pump system special care was taken to make the transport of blood as gentle as possible in order to reduce hæmolysis as much as possible. This was achieved by choosing suitable material, by making the pump tubes (fig. 1) so wide that even a maximum stroke-volume will not

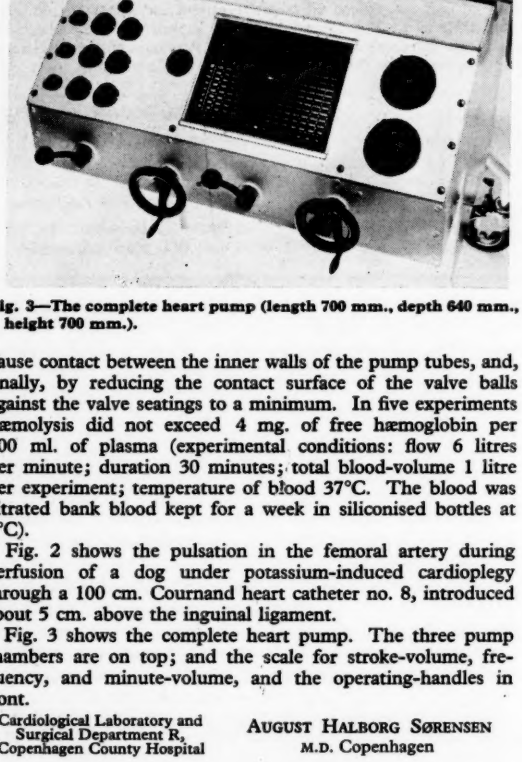

Fig. 3—The complete heart pump (length 700 mm., depth 640 mm., height 700 mm.).

cause contact between the inner walls of the pump tubes, and, finally, by reducing the contact surface of the valve balls against the valve seatings to a minimum. In five experiments hæmolysis did not exceed 4 mg. of free hæmoglobin per 100 ml. of plasma (experimental conditions: flow 6 litres per minute; duration 30 minutes; total blood-volume 1 litre per experiment; temperature of blood 37°C. The blood was citrated bank blood kept for a week in siliconised bottles at 4°C).

Fig. 2 shows the pulsation in the femoral artery during perfusion of a dog under potassium-induced cardioplegy through a 100 cm. Cournand heart catheter no. 8, introduced about 5 cm. above the inguinal ligament.

Fig. 3 shows the complete heart pump. The three pump chambers are on top; and the scale for stroke-volume, frequency, and minute-volume, and the operating-handles in front.

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A STANDARD, CARTRIDGE-FORM, COTTON-WOOL AIR-FILTER FOR PRESSURE-STEAM STERILISERS

THE need for efficient air-filtration for hospital sterilisers is generally realised, but many sterilisers lack adequate filters and are merely fitted with a tube or container designed to hold cotton-wool. While sterile, non-absorbent cotton-wool, correctly used, gives safe filtration,[1] the incorrect use of cotton-wool and the use of absorbent wool or materials such as cotton-gauze gravely endanger sterilisation. The Medical Research Council working party on pressure-steam sterilisers reviewed the problems involved.[2]

1. Rice, H. M. *Lancet*, 1958, ii, 1275.

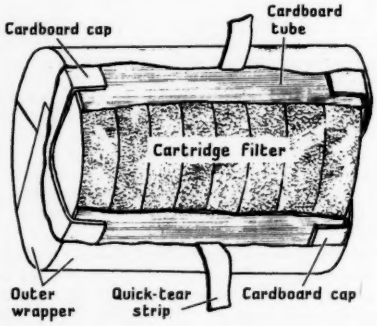

Fig. 1—Diagram of structure of cotton-wool cartridge-filter.

To obviate human error in the use of cotton-wool for air-filtration a standard filter, in cartridge form,[3] suitable for use with all pressure-steam sterilisers, has been evolved. It consists of eight circular layers of non-absorbent cotton-wool in a cardboard tube three inches long, capped at both ends. The unit is sealed in paper (fig. 1) and sterilised in a high-vacuum autoclave. A special filter-holder [3] is required, which should be fitted to the steriliser horizontally, at eye-level and in an accessible position. For use, the paper wrapper of the filter-cartridge is opened by pulling the quick-tear strip and discarded, together with one end-cap. The open end of the tube is placed in the mouth of the filter-holder, and the other end-cap is removed, when the filter can be pushed through the tube into the holder (fig. 2). The tube is then discarded and the lid of the holder shut. The only part of the filter to be contaminated is the outer face, the inner surface remaining completely untouched. The interior of the filter-holder tapers to a knife-edge seal, above the perforated base-plate, to ensure an air-tight fit when the filter is pushed home. The air-seal is automatically reinforced by compression of the cotton-wool, on vacuum-release. The filter is changed daily and is left in the holder after use, to prevent contamination of the air-line.

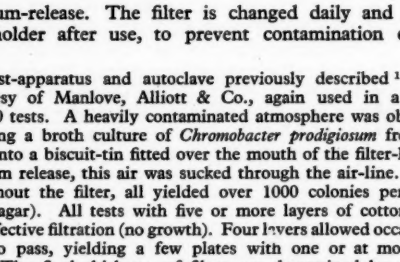

Fig. 2—Method of inserting filter into filter-holder. The cover of the filter-holder is lowered once the filter has been pushed home and the cardboard tube is removed.

The test-apparatus and autoclave previously described [1] were, by courtesy of Manlove, Alliott & Co., again used in a series of over 80 tests. A heavily contaminated atmosphere was obtained by spraying a broth culture of *Chromobacter prodigiosum* from an atomiser into a biscuit-tin fitted over the mouth of the filter-holder. On vacuum release, this air was sucked through the air-line. Controls, without the filter, all yielded over 1000 colonies per plate (nutrient agar). All tests with five or more layers of cotton-wool showed effective filtration (no growth). Four layers allowed occasional bacteria to pass, yielding a few plates with one or at most two colonies. The final thickness of filter was determined by adding a 50% safety-margin to the minimum effective thickness (five layers).

It is hoped that this filter, by ruling out the use of the wrong type of cotton-wool, by ensuring its sterility, and by giving uniform and safe air-filtration, will make a real contribution to the practice of hospital sterilisation.

I wish to thank Vernon & Co. Ltd., of Preston, and Steritec Ltd., of Nottingham, who have collaborated in evolving the 'Sterifilta' filter and filter-holder, respectively; Dr. J. C. Kelsey for suggesting the use of *Chr. prodigiosum* as the test-organism; and Mr. C. A. Durrant, F.I.M.L.T., for help with the bacteriology.

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2. M.R.C. working party report on pressure-steam sterilisers. *ibid.* 1959, i, 425.
3. Provisional patent 10587/59.

Reviews of Books

Blindness in West Africa

F. C. RODGER, M.D., CH.M., D.O.M.S., research professor of ophthalmology, Aligarh University, India; director, ophthalmological survey, Royal Commonwealth Society for the Blind. London: H. K. Lewis (for Royal Commonwealth Society for the Blind). 1959. Pp. 262. 70s.

IN parts of tropical Africa and the Americas, onchocerciasis is a cause of blindness seldom found elsewhere. Dr. Rodger and his assistants worked on this problem for four years in Northern Ghana, Northern Nigeria, and the Cameroon Highlands, and this book records their findings, which are of great interest and importance, and the result of painstaking labour. Dr. Rodger is to be congratulated on an achievement which will, we hope, stimulate not only other workers but also Governments.

The introduction says the book was written so that interested lay persons could appreciate parts of it: this may be a mistake, for it is often as hard for a man to write for two publics as it is for him to serve two masters. The determination of the incidence of blindness will arouse comment. The methods used are not described, but it is stated that " a general picture of the incidence of blindness in West Africa will emerge from the analysis now to be given ". Many villages and townships were visited and perhaps a more precise and valuable picture would have emerged from a study of a smaller sample in greater detail.

The section on onchocerciasis is full and the detailed descriptions of its syndromes are very valuable, though not all workers will agree that onchocerciasis alone is responsible for all these conditions. Thus, there is resistance against diagnosing punctate keratitis as onchocercal even when conjunctival biopsies are positive, but with " chronic, non-specific uveo-retinitis . . . the association with an anterior lesion of onchocerciasis points to the diagnosis ". Elsewhere, regarding onchocercal chorioretinopathy, it is pointed out that " it is remarkably difficult to distinguish between this lesion and a chorioretinitis due to syphilis and tuberculosis ".

The method of assessing the individual density figure for infection is also open to criticism, because an arbitrary score is given for finding onchocercal microfilariæ in different parts of the body. It is perhaps unfortunate too that the Southern Cameroons, where onchocerciasis is highly endemic, but where the climate is very different from the Northern regions, was not included in the study.

The reviews of the literature reveal that many of the subjects remain highly controversial, but this book stands out as a lively and helpful contribution to the forum.

Family and Class Dynamics in Mental Illness

JEROME K. MYERS, associate professor of sociology, Yale University; BERTRAM H. ROBERTS, late assistant professor of psychiatry, Yale University. New York: John Wiley. London: Chapman & Hall. 1959. Pp. 295. 56s.

THIS interesting book describes the second and rather less auspicious part of an extensive sociopsychiatric survey. In the now celebrated earlier part, Professor Hollingshead and Professor Redlich [1] used the census method to demonstrate that the prevalence, type, and treatment of psychiatric disorder was related to class structure. This study examines 50 families in detail to discover different social and dynamic factors at work between different classes (in which it is successful) and the relationship of social mobility to psychiatric illness (in which it is a little less successful).

In brief, class-5 illness tended to arise in a troubled setting, much preoccupied with material survival, where Father acted as a powerful uninterested authority figure and where conflicts were acted out in antisocial ways. In class 3, though Mother was more dominant, control of the children was better and family concern was more with social ambition: obsessional and neurotic traits predominated here. Schizophrenic children showed a " submissive life pattern " and were noted as " different " from the others, but on the other hand they were submitted to more pressures and stresses at all levels than the neurotics. It was suggested that, coming from homes of more disturbed parents, and receiving less affection, they identified with the more disturbed parent (usually Mother) and relieved the difficult situation by withdrawing from it. Much valuable information is also given on parental and sibling attitude, sexual difficulties, and psychiatric symptomatology.

Although this book maintains its predecessor's extremely high standard of scholarship and production, it is of limited value for several reasons: it is limited to neurotics and schizophrenics of social classes 3 and 5 only, but even so the numbers and distribution are so restricted as to detract from wider application of the findings. It is also limited to treated cases, to white adults of 22–44, and to those willing to cooperate. The data, furthermore, were retrospective, and there were no controls. These defects, however, are understandable in the face of the immense practical difficulties in the way of this type of research. The next stage in descriptive psychiatric work is to make quantifiable observations in the home setting, and this excellent study, an " exploratory " one as the authors' admit, will be a signpost to future workers.

1. See *Lancet*, 1958, ii, 888.

The Chemistry of Heredity

S. ZAMENHOF, PH.D., associate professor of biochemistry, Columbia University, New York. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959. Pp. 106. 34s.

COMPRESSING what is known of the chemistry of heredity into 80 pages, while retaining some semblance of cohesion, is a task not to be undertaken lightly, and Dr. Zamenhof may be said to have rushed in where other investigators have remained at the bench.

He introduces his monograph with the surprising comment that " The very thought of reading a book about the Chemistry of Heredity is likely to encounter a great deal of resistance. The word ' Chemistry ' is often inimical and reminds one of a lot of difficult or boring moments in one's school days." This may explain why he has adopted a style of lightweight simplicity which seldom attempts to penetrate below the surface; and why he occasionally introduces exclamatory comments and often italicises words and phrases.

Nucleic acids, mutation, and cytoplasmic inheritance are among the subjects fleetingly but sensibly discussed. The chapter on nucleic acid, although too brief, is clear and up to date and it is apparent that the author, as a distinguished investigator who has made notable contributions to the subject, is a capable critic and interpreter of the recent scientific literature. The often neglected work of Griffith, which preceded the definitive studies of Avery, is admirably emphasised in the account of transformation, and this section is one of the best in the book. The section on hereditary defects in man is contained in 8 pages. Alkaptonuria, albinism, galactosæmia, and sickle-cell anæmia are among the subjects that are discussed rather too briefly.

A well-chosen bibliography of 185 articles is the most valuable asset of this small monograph, one of a series of American Lectures in Living Chemistry. The book, well produced but expensive, may serve as an accurate introduction to a subject which urgently requires a more rigorous treatment.

Bibliography of Cancer Produced by Pure Chemical Compounds

A Survey of the Literature up to and including 1947. OTTO NEUBAUER, M.D., formerly professor, Munich University. London: Oxford University Press. 1959. Pp. 604. 42s.

IN a foreword, the late Sir Ernest Kennaway remarks that " at the present time, the progress of every science tends to be impeded by the accumulation of its own literature . . .". Probably of no other branch of science is the statement more

true than of cancer research. The result of the late Professor Neubauer's courageous undertaking in cataloguing, indexing, and classifying what is virtually the major part of experimental cancer research up to 1947 is a unique achievement. For apart from the thoroughness with which references were pursued, and the tenacious accuracy with which they are presented, the bibliography is more comprehensive than anything that has been attempted in this subject since the early exhaustive reviews of tar cancer by Woglom (1926) and Seelig and Cooper (1933). The confluence and interplay of the various scientific disciplines in cancer research is clearly shown.

The work consists of two main parts—an author index and a subject index, together with a list of tumour sites. The subject index includes an English translation of the titles of papers which are in another language. This part is divided into 32 sections which deal with the various parameters involved in carcinogenesis, with the chemical and physical nature of the agents, their mode of administration, their metabolism, their effects on the organism, and intrinsic and extrinsic influences on their course of action. The sections are subdivided according to the chemical nature of the carcinogen, aromatic hydrocarbons, azo-compounds, &c., and in such subdivisions the papers are arranged in chronological order, bringing out the history of the development of the subject. It was the era of the aromatic hydrocarbons.

Since 1947 many agents and modes of tumour production have been discovered—e.g., films of high polymers, alkylating agents, certain alkaloids, and such bizarre carcinogens as tricycloquinazoline and 4-nitroquinoline-N-oxide, not to mention intermittent anaerobiosis. (We hope the bibliography will be supplemented with such new data at intervals in the future.) A minor criticism might be directed against the representation and inclusion of heated fats and oils, non-ionising radiation, and certain virus preparations as pure chemical compounds.

Parasites and Parasitic Infections in Early Medicine and Science

R. HOEPPLI, M.D., D.SC., formerly professor of parasitology, Peking Union Medical College. Singapore: University of Malaya Press. 1959. Pp. 526. 63s.

AFTER a lifetime of valuable contributions to parasitology, the distinguished author now brings together in this attractive volume the fruits of many years' historical studies. Although much of the material is Chinese, contributions are also included from Borneo, Malaya, Fiji, Tahiti, and Europe, so that part I is an extensive account of the history of parasitology from ancient times to the middle of the 17th century, and in part III some publications as late as the 19th century are included. Part II deals with special parasitological subjects, such as malaria, dysentery, scabies, and leeches in Chinese medicine, Chinese anthelmintics, and the remarkable habit of eating lice. An interesting appendix discusses the part played by parasites in history, in which syphilis, trypanosomiasis, malaria, hookworm disease, and schistosomiasis are included. Not the least valuable items are the references to the literature at the ends of each section and in the footnotes. The Chinese characters have been written by Mr. Choo Yew-Wai.

Professor Hoeppli refers to "the ticklish question whether Adam and Eve in Paradise had lice"; and to the writer in *The Gentleman's Magazine* for 1746, quoted also by Zinsser in his *Rats, Lice and History*, who remarked, with all the charm of the outlook of that time, that "we can hardly suppose that it (the louse) was quartered on . . . the neatest pair (if we may believe John Milton) that ever joined hands. And yet, as it disdained to graze the fields or lick the dust for sustenance, where else could it have had its subsistence?" And yet if, as Hoeppli tells us, Herodotus recorded the habit of eating lice, which is still "comparatively widespread today", can we blame this "neatest pair" if they did not disdain to eat companions who themselves disdained to lick the sustaining dust?

But this is a lighter side of this careful and well-documented book. It abounds in information and shrewd observation, and there are 23 plates, which include the first illustrations of *Cysticercus pisiformis*, a tapeworm, and an itch-mite, as well as figures of other parasites and photographs of the methods of spirit-doctors.

Isotopic Tracers (2nd ed. London: University of London, Athlone Press. 1959. Pp. 524. 52*s*. 6*d*.).—The great value of the first edition of this book, by Dr. G. E. Francis, Dr. W. Mulligan, and Prof. A. Wormall, was that it was written by a team of biochemists in touch with medical and veterinary matters. They knew that medically qualified research-workers often have limited experience in physics and mathematics, and they knew the kind of problems in which they were interested. In the five years since the first edition there has been much expansion in the application of tracer techniques, and many changes in the practical details. The sections on instrumentation and practical methods have been considerably expanded, and part II of the book gives a list of exercises that could be used for an "instructive and interesting practical isotope course". The greater part of the book is taken up with description of the available isotopes, both stable and radioactive, their properties, preparation, and measurement; and the preparation of labelled compounds is fully dealt with. Many examples of the use of isotopic tracers in biological and medical research are discussed. The importance of understanding the hazards of using radioactive isotopes is emphasised, and practical precautions against unnecessary exposure are set out. Fourteen short appendices provide useful notes on the characteristics of available isotopes and where they can be obtained, on terminology, and on some practical techniques; some mathematical information is also included. Useful bibliographies are provided at the end of each chapter. Any doctor preparing to embark on isotope-tracer research should begin by studying this well-produced and low-priced book, and all users of these techniques will find it a valuable handbook.

Blood Clotting Factors (Proceedings of the 4th International Congress of Biochemistry, Vienna, 1958, symposium x. London and New York: Pergamon Press. 1959. Pp. 254. 70*s*.).—This is one of 15 volumes recording the proceedings of what must have been a mammoth conference. Edited by E. Deutsch, it contains 16 articles in English and 5 in German on biochemical researches concerned with blood-clotting factors. The papers vary in length from 25 lines to 37 pages; a few of them have summaries. They are mostly very technical and only of interest or even intelligible to those engaged in this work, and many of them are devoted to progress reports about attempts to purify or isolate clotting factors—for example, the paper by Brinkhous and Wagner on the anti-hæmophilic factor. A paper by Gross, Löhr, and Waller, of Marburg, strikes a new note by exploring the carbohydrate-metabolising enzymes of platelets and suggesting that Glanzmann's thrombasthenia is associated with a deficiency of these enzymes. A. J. Quick reiterates his views on the properties and formation of tissue-thromboplastin and its relation to plasma-thromboplastin. He also points out that erythrocytes contain a phospholipid clotting agent which can be applied to the diagnosis of hæmophilia B (Christmas disease). A paper by Biggs and Bidwell, of Oxford, on the kinetics of blood-thromboplastin formation emphasises the difficulties of interpreting results while testing systems are still crude. Lorand and coworkers at North Western University, Illinois, have produced a brand-new factor, "fibrin-stabilising factor". This volume may be a useful reminder to those who attended the conference, but we doubt whether it fully justifies the trouble and expense devoted to its publication, since any work that is not purely transitory will surely be published sooner or later in medical or biochemical journals.

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Mucoviscidosis in Adults

OUR children's diseases are growing up at last—a reflection perhaps of better pædiatric management as well as of improved diagnostic methods in adult life. Thus, symptoms and signs in adults reminiscent of the childhood manifestations of mucoviscidosis (or fibrocystic disease) have led several workers to search for this condition in adult hospital populations; and KOCH, of Giessen, has now reviewed no less than 84 such cases.[1] Besides the surprising frequency of the disease, several important facts emerge from his careful analysis. Relatives of 41 patients showed some clinical or laboratory evidence of mucoviscidosis—a finding which suggests to KOCH autosomal dominant inheritance with a fairly high penetrance rather than a recessive mode of transmission. (He does not consider the possibility of *formes frustes* in heterozygotes.[2 3]) Many of his patients and their relatives, moreover, also had peptic ulceration —a recognised but exceedingly rare complication of the illness in childhood. This prompted him and his associates to investigate five groups of adults: 32 healthy university students; 35 cases of gallbladder disease with suspected pancreatic involvement; 43 patients with peptic ulcer; 88 patients admitted to hospital on account of various unrelated complaints; and 68 close relatives of the 41 mucoviscidosis patients. The diagnosis was based on clinical evidence, estimation of sweat-electrolytes, and analysis of pancreatic enzymes—mainly in duodenal aspirates.

Though its physiological mechanism and ætiological significance are still undecided,[4–7] the high salt content of sweat of patients with mucoviscidosis is a valuable diagnostic finding. For screening purposes, so long as its limitations are appreciated, the finger-print test is a simple and attractive ward procedure [8]; but for accuracy sweat must be collected in plastic bags and subjected to chemical analysis.[9 10] In health sweat very rarely contains more than 60 mEq. chloride, 70 mEq. sodium, or 20 mEq. potassium per litre—there was one instance in KOCH's survey—and higher concentrations than these were not found in the other illnesses investigated at the Giessen clinic. Pancreatic enzymes are best analysed in fractional samples; and especial attention must be paid to an unequal depression of the various enzyme activities. The four estimated by KOCH were amylase, trypsin, lipase, and carboxypeptidase [11–13]; and in 11 out of 18 patients with mucoviscidosis the activity of one or another was depressed. This contrasts with the findings in gallbladder disease associated with pancreatitis, in which the activity of all duodenal enzymes is often uniformly low. Of 43 peptic-ulcer cases the values were normal in about half; the other half had dissociated pancreatic insufficiency, carboxypeptidase activity being diminished most commonly and lipase activity only rarely. (KOCH mentions a 60-year-old man with high-normal amylase and trypsin levels, almost complete absence of carboxypeptidase and lipase activity, and a raised sweat-electrolyte excretion; he had two recent ulcers on the lesser curve of the stomach and long-standing duodenal scarring.)

These curious findings naturally suggest the possibility of bias in the selection of the case-material; for, as KOCH rightly observes, our diagnostic methods for the detection of mucoviscidosis are by no means foolproof. On the other hand, valuable information can be had from family studies. Of the 68 relatives of the 41 cases of mucoviscidosis, only 9 were entirely free from symptoms, signs, or laboratory evidence of the disease. 17 of the mucoviscidosis patients and 19 of the relatives available for investigation had peptic ulceration. The prevalence of peptic ulcer in families with mucoviscidosis thus appeared to be ten times greater than that in the normal population.[14] Approaching this association from another angle KOCH investigated 43 unselected ulcer patients who had come to the clinic for the treatment of peptic ulcer. Comparing them with the 36 ulcer cases from mucoviscidosis families he found little difference in their age and sex distribution and in the age at onset of symptoms. The proportion of duodenal and gastric ulcers, however, was 25 : 18 in the unselected ulcer series and 31 : 5 among patients from mucoviscidosis families; and sweat-electrolyte disturbances were twice as common and pulmonary emphysema three times as common in the mucoviscidosis group. Pancreatic-enzyme activity was related little if at all to the position of the ulcer and possible pancreatic penetration. About half the unselected ulcer cases exhibited one or more of the characteristic features of mucoviscidosis. KOCH also formed a clinical impression of certain differences between peptic-ulcer patients with mucoviscidosis and those without. The former group included a high proportion of middle-aged men with duodenal ulcers who commonly had multiple ulcers, had otherwise unexplained cachexia, dehydration, low blood-pressure, and a tendency to cardiovascular collapse, and who, since a fairly early age, had had pulmonary emphysema, cyanosis, and clubbing of the fingers. In these patients the characteristically raised sweat-electrolyte levels, a positive family history for mucoviscidosis, and dissociated pancreatic insufficiency often confirmed his clinical suspicion.

If the emergence of mucoviscidosis from the children's ward has already yielded one surprising link with a common illness of middle and later life, others are likely to follow. We have hinted at the great diversity of some of the late manifestations of the disease [7]; and many may

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2. Smoller, M., Hsia, D. Y.-Y. *A.M.A. J. Dis. Child.* 1959, **98**, 277.
3. Childs, B. Report of the 18th Pediatric Research Conference, Columbus, Ohio; 1956, p. 87.
4. di Sant'Agnese, P. A. *Amer. J. Med.* 1956, **21**, 406.
5. Peterson, E. M. *J. Amer. med. Ass.* 1959, **171**, 1.
6. Roberts, G. B. S. *Lancet*, 1959, ii, 964.
7. *ibid.* p. 955.
8. McFarlane, J. C., Norman, A. P. *Brit. med. J.* 1957, ii, 274.
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10. Bohn, H., Koch, E., Koch, F., Rick, W., Rauh, R. *Dtsch. med. Wschr.* 1959, **84**, 1139.
11. Andersen, D. H., Early, M. V. *Amer. J. Dis. Child.* 1942, **63**, 891.
12. Nothman, M. M., Pratt, T. D., Benotti, J. *J. Lab. clin. Med.* 1948, **33**, 833.
13. Schwachman, H. *A.M.A. J. Dis. Child.* 1956, **95**, 347.
14. Doll, R. *Ann. Eugen.* 1949, **14**, 135.

still be unrecognised. Even the classical manifestations of the childhood illness tend to escape detection in adults. The respiratory syndrome can become almost indistinguishable clinically from other chronic lung diseases associated with the formation of large quantities of viscid sputum (notably infective asthma) [15–17]; but it is worth remembering that in mucoviscidosis secondary staphylococcal infection is said to be particularly common.[9 18] This organism thrives in a medium containing a higher concentration of salt than is favoured by most bacteria; and possibly the salt-rich salivary and bronchial secretion of patients with mucoviscidosis inhibits potential competitors. On the other hand, after long-continued treatment with a wide range of antibiotics other organisms—mainly proteus and pseudomonas—are now being isolated with increasing frequency, and we can certainly expect a growing incidence of monilia infection. The conditions created by long-standing fibrocystic disease in the lungs are ideal for the development of cor pulmonale: but even direct involvement of the myocardium cannot yet be excluded.[19]

Of the less common features of the disease, biliary cirrhosis merits more attention than it receives at present. It should be added to the growing list of causes of jaundice in the newborn; and in adolescence and adult life it must be considered as an ætiological factor in portal hypertension.[20–23] In these cases bleeding from œsophageal varices is commoner than hepatic failure. Electrolyte imbalance is another complication that requires the utmost care for detection, assessment, and management. Patients with mucoviscidosis can lose alarming amounts of sodium, potassium, and chloride in their sweat—far more than we generally allow for in making up fluid-balance charts—and often this has to be added to other losses through diarrhœa and viewed against a background of chronic respiratory acidosis. The task of maintaining balance is indeed formidable; and even minor operations provide a severe test in applied physiology.[17] Steatorrhœa has long been recognised as one of the cardinal features of mucoviscidosis in childhood; but adults too deserve a second look. We know too little of this common and disabling condition to dismiss the diagnosis of mucoviscidosis on the ground that routine pancreatic-function tests are negative. The unusual type of inflammatory reaction reported by MARKS and ANDERSON [24] may prove characteristic. Their middle-aged patient with longstanding pulmonary suppuration and steatorrhœa also had choroiditis, vitreous opacities, and enlarged submandibular salivary glands—pointers to further possible ramifications of this puzzling and perhaps not so rare syndrome.

15. Noah, J. *Amer. J. Med.* 1959, **27**, 485.
16. Weeks, M. M., Brown, G. A. *Arch. Dis. Childh.* 1958, **33**, 74.
17. Kulczycki, L., Craig, J. M., Schwachman, H. *New Engl. J. Med.* 1957, **257**, 203.
18. Harford, C. G. *Amer. J. Med.* 1959, **27**, 490.
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23. Norris, T. St. M. *Proc. R. Soc. Med.* 1957, **50**, 507.
24. Marks, B. L., Anderson, C. M. *Lancet*, Feb. 13, 1960, p. 365.

Staphylococci in the Family

No other microorganism can compare with the staphylococcus in its capacity to persist as a parasite in individuals or communities. This persistence has been well demonstrated by RoODYN in a seven-year study of families attending the Woodberry Down Health Centre. In 1951–58 RoODYN [1] studied seventeen families in which multiple staphylococcal infections arose. In eleven of these families phage-typing showed that the same staphylococcus had spread from person to person in the family. In two families a single strain of staphylococcus persisted for over six years. In each of these two families 1 member was prone to recurrent lesions, and although both were nasal carriers it was only when they developed sepsis that other members of the family became infected. In a second paper RoODYN [2] describes a study of 81 patients who first presented with staphylococcal infection in 1951–52 and were kept under observation for the following seven years. In this period 23 of the patients had recurrences; in 14 cases there was only a single recurrence a few weeks after the initial lesion, but 9 of the patients had repeated attacks of boils. From a study of the phage type of staphylococcus isolated from successive infections in these 9 patients it was shown that the same organism had persisted for over six years in 2 cases, for four to five years in 5 cases, and for one and a half to three years in 2 cases. Identical strains were isolated from the nose and lesion of 16 of the 23 patients who had recurrent infections. In 5 of these patients the nasal carriage persisted for more than four years. 2 patients were persistent skin carriers without being nasal carriers.

To what extent does this situation in the family differ from that in hospital? There, too, staphylococci may persist; and the same strain of staphylococcus may predominate in a hospital community for many years, although the composition of the community is constantly changing.[3 4] One obvious difference is the greater severity of the infection in the hospital. Patients in hospital are of course peculiarly susceptible to infection; but many would affirm that at any rate some strains of hospital staphylococci not only are more likely to be resistant to antibiotics but also are of enhanced virulence.[5–8]

There is, of course, a two-way traffic. Many patients —particularly babies—take hospital staphylococci home in their noses and may retain them for many months.[9 10] This is reflected in the increasing incidence of penicillin-resistant strains isolated in general practice.[11–13] Possibly

1. Roodyn, L. *J. Hyg., Camb.* 1960, **58**, 1.
2. Roodyn, L. *ibid.* p. 11.
3. Rountree, P. M., Barbour, R. G. H. *J. Path. Bact.* 1951, **63**, 313.
4. Barber, M., Hayhoe, F. C. J., Whitehead, J. E. M. *Lancet*, 1949, ii, 1120.
5. Rountree, P. M., Freeman, B. M. *Med. J. Aust.* 1955, ii, 157.
6. Beavan, D. W., Burry, A. F. *Lancet*, 1956, ii, 211.
7. Shooter, R. A., Smith, M. A., Griffiths, J. D., Brown, M. E. A., Williams, R. E. O., Rippon, J. E., Jevons, M. P. *Brit. med. J.* 1958, i, 607.
8. Barber, M., Dutton, A. A. C., Beard, M. A., Elmes, P. C., Williams, R. *Brit. med. J.* Jan. 2, 1960, p. 11. See *Lancet*, Jan. 16, 1960, p. 157.
9. Ludlam, G. B. *J. Hyg., Camb.* 1953, **51**, 64.
10. Hurst, V. *ibid.* 1957, **55**, 299, 313.
11. Roodyn, L. *Brit. med. J.* 1954, ii, 1322.
12. Roodyn, L. *Proc. R. Soc. Med.* 1956, **49**, 263.
13. Gould, J. C., Cruikshank, J. D. *Lancet*, 1957, ii, 1157.

strains carried in the nose in the absence of sepsis lose some of their virulence.

Conversely patients and possibly visitors may bring staphylococci with them into hospital. A patient with a staphylococcal lesion, however small, should if possible be isolated; but it is doubtful whether anything is gained by treating all nasal carriers on admission. If strains spreading in a hospital are really of enhanced virulence, nasal carriage of a less virulent strain might be a protection. As for visitors, most workers regard these as a negligible source of danger; and, although this view has recently been questioned by BOYD,[14] unless they have boils or other lesions it seems unlikely that they are a serious added menace in a hospital already riddled with staphylococci.[15 16]

The complexity of the subject is again apparent in a new investigation by BERNSTEIN and MCDERMOTT[17] from the Bellevue Hospital, New York. They studied the transfer of strains of *Staphylococcus aureus* in the nasopharynx of two groups of patients admitted to a large (40-bedded) medical ward. One group of 130 patients received no antibiotics during their stay in hospital and the second group of 120 patients were treated with tetracycline. On admission both groups had a nasal carrier-rate of approximately 34%. Subsequently the carrier-rate increased by 11% in the first group and by 30% in the group treated with tetracycline. Substitution of one strain of staphylococcus by another took place in 12 of 44 original carriers in the untreated group and 24 of 41 original carriers in the tetracycline group. Thus a new strain of *Staph. aureus* was acquired in 29% more of the tetracycline-treated group than among those having no antibacterial treatment. In neither group did the presence of staphylococci in the nasopharynx on admission protect the patient against the acquisition of new strains.

A further point of some interest is that although, as might be expected, the tetracycline-treated patients tended to be colonised by drug-resistant strains, this was not so with the untreated patients, who picked up twice as many drug-sensitive as drug-resistant strains (resistant to what drugs was not stated). This finding seems somewhat in conflict with the observation of many investigators, who have shown that nurses, newborn babies, and maternity and other patients, none of whom were on antibiotic treatment, tended to become nasal carriers of drug-resistant staphylococci after a short stay in hospital.[3 4 18 19] BERNSTEIN and MCDERMOTT[17] do not mention the source of the "acquired" strains. It would be interesting to know whether they came from other patients or from nurses, and whether the nurses tended to carry drug-resistant staphylococci. In such a large medical ward the influx of new strains may be sufficient to prevent the emergence of a predominant hospital staphylococcus. It is certain that experience in a medical ward, where presumably staphylococcal sepsis was rare, cannot be compared with experience in surgical or maternity wards, where staphylococcal infection is relatively common.

14. Boyd, A. M. *Brit. med. J.* Feb. 20, 1960, p. 563.
15. Steingold, L., Ashworth, L. *ibid.* March 19, 1960, p. 878.
16. Lowbury, E. J. L., Jackson, D. M. *ibid.* April 16, 1960, p. 1203.
17. Bernstein, C. A., McDermott, W. *New Engl. J. Med.* 1960, **262**, 637.
18. Barber, M., Wilson, B. D. R., Rippon, J. E., Williams, R. E. O. *J. Obstet. Gynæc. Brit. Emp.* 1952, **60**, 476.
19. Brodie, J., Sommerville, T., Wilson, S. G. F. *Brit. med. J.* 1956, i, 667.

Not too Big

EQUIPMENT is more easily replaced than buildings, and many clinical departments working in dingy and inconvenient surroundings are nevertheless able to offer their patients the latest forms of treatment. To the mental hospital outdated and ugly buildings are a much heavier handicap, because the patient's surroundings are relatively important. Whereas in other specialties equipment has altered with changes in practice, in psychiatry monolithic buildings have often hampered the introduction of new ideas and procedures. That so much has been done, despite the discouragement of bricks and mortar and the influence of asylum baroque, is proof of the strength of these ideas. But progress will become quicker and experiment more hopeful if full advantage is taken of even the present modest opportunities for hospital building. Psychiatric services and architecture is thus a timely choice of subject for the first [1] of a series of occasional papers which the World Health Organisation is to publish to stimulate international thinking and discussion. Of the three authors Dr. Baker is medical superintendent of an English mental hospital, Dr. Sivadon of a group of French ones, and Mr. Llewelyn Davies the director of the Nuffield Foundation's division of architectural studies, and they have combined to offer practical advice and a thoughtful reassessment of principles.

Unfortunately many mental hospitals were built at a time when the pattern of care was custodial. Large hospitals in large grounds were accordingly erected in remote rural areas. But yesterday's advantage is often today's defect. The aim of psychiatry is no longer to guard and soothe the patient, but to help him to return to everyday life. For this the old-fashioned hospital is usually ill suited—forbidding in appearance, inaccessible by public transport, difficult to staff, expensive to maintain. For the vulnerable patient, as Dr. Baker and his colleagues point out, there are still more drawbacks. When the patient arrives the pretentious façade of the massive block will tend to make him feel small and frightened. Inside he will find long corridors bewildering in their similarity. In the ward he will find no privacy, but perhaps the stale smell of inadequate sanitary arrangements. The room where he lives will be either large and lofty or a tiny cell; neither will have normal domestic proportions.

The needs of the mental patient vary with the stage of his illness. In the acute phase he requires a small secure area and the reassuring support of one person. As he improves he should be introduced to a small family-sized group, and gradually encouraged to widen the ambit of his activities and contacts until he is sharing in all the life of the hospital in preparation for his return to the community. The amorphous mental

1. Baker, A., Llewelyn Davies, R., Sivadon, P. Psychiatric Services and Architecture. W.H.O. public health paper, no. 1. Geneva. 1959. Pp. 59. 2*s*. 6*d*.

hospital, in the past at any rate, was a form of blunderbuss therapy. Little attempt was made to match the patient and his setting. Dr. Baker has described [2] how much can be achieved, even under the stringencies of real life, in an unwieldy hospital if it is broken up into smaller units and communities. Offered the freedom of planners, he and his colleagues have drawn up a workmanlike scheme for diverse buildings to offer diverse care:

The *outpatient clinic and early-treatment centre* are the basic unit, and need only simple accommodation: a waiting area which can be temporarily divided for informal groups, a secretary's office, two treatment rooms, and two consulting-rooms, which should not be so large as to frighten the patient, which yet should look like a consulting-room, but which should not display any alarming apparatus. In country districts some might have a small inpatient unit of 6 beds. The *day hospital* can be grouped with the outpatient clinic, but should be self-contained. It would include more small rooms for treatment and larger rooms for group therapy, occupational therapy, or physiotherapy, a dining-room, and a social club.

The *psychiatric hospital* proper should be a "social field" of 300 patients and 12 doctors. It should encourage the patient's progress by varying his living conditions. At first he will need a small individual room or cubicle; later he will join a small group of 4–8 people and gradually pass to larger groups of up to perhaps 30. Ward units should be divisible into areas suitable for these groups. The ward should offer security, reassurance, and some privacy. The patient should have some place to keep his own belongings. He should himself manage door-closing devices, wash-basins, and water-closets. Where security is essential, precautions should be simple and unambiguous; devices which only give an illusion of liberty may make the patient feel that he is being deceived. Familiarity enhances security and plans of the hospital should be posted in each ward. Prominent clocks, calendars, and timetables of the day's activities will help the patient to reorient himself in time and place.

Some patients will need a small workroom inside the ward. Small workshops will take patients from several nearby wards. Larger more distant workshops will draw patients from the whole hospital. A central part of the hospital would offer opportunity for communal life—a restaurant, little shops, the hairdresser, library, lecture-room, chapel. The medical services would also have a centre, which should be in a separate building apart from the wards and the social centre. Special units are proposed for special groups, such as mothers and babies, children, and old people.

For many patients an *aftercare home* will be the first step towards rejoining the community. It should be independent of the hospital, should be small, and should look similar to other houses in the town. For this purpose conversion has some advantage over new building. For the long-stay schizophrenic a *working settlement* of 20–50 patients is proposed.

These therapeutic principles impose principles of design. Buildings must provide a gradation of spaces and flexibility in their arrangements. They should suggest a semidomestic environment, such as a residential college, where a sense of purpose is explicit. The wards should be regarded as living quarters for patients and other services should be housed in separate buildings grouped imaginatively over the site in a variety which will help to reeducate the patient in his grasp of space. But the overriding principle that emerges is the need for modesty in size. As the authors put it, "many cultures will feel the need to provide large and imposing buildings to show their prowess and ability. Such building could house research institutions, library facilities, and congress halls, but they should not be used for hospitals."

2. Baker, A. *Lancet*, 1958, ii, 254.

Annotations

GUT

In 1937 the late Sir Arthur Hurst formed a small club of thirty-six colleagues interested in gastroenterology. This group became the nucleus of the British Society of Gastroenterology, which has prospered with the development of the specialty. As the size and authority of the society grew, so did the need for a British journal devoted to the subject. In 1958 the society resolved that a quarterly journal be prepared, and the first issue has appeared lately.

Entitled with unelaborate brevity *Gut*,[1] the journal is edited by Mr. Harold Edwards and Dr. F. Avery Jones, with a committee of other experts. In a foreword, Mr. Edwards stresses the integration of all types of general medical and surgical knowledge which is required to resolve gastroenterological problems. The first issue, with its varied contents, is promising.

In an account of blood-group distribution in peptic ulcer and gastric cancer, Doll et al.[2] emphasise the susceptibility of patients of blood-group O to stomal ulceration, but they have failed to confirm previous observations that antral gastric ulcers and neoplasm are especially liable to develop in subjects of blood-group A.

From two necropsy surveys covering some 20,000 examinations—one retrospective from Leeds and the other prospective from various parts of the country—Watkinson [3] concludes that ulcer frequency in the general population is best estimated by studying the prevalence of ulcer in patients who have died from causes other than ulcer.

The increasing recognition of the relation of hormonal secretion to gastrointestinal diseases is reflected in several articles. One describes the effect of corticotrophin, cortisone, prednisone, and aldosterone on secretion from denervated gastric pouches in dogs.[4] All these agents, given in pharmacological doses, increased the volume of acid in the gastric secretions and reduced the content of pepsin, sodium, and potassium. The augmentation of secretion, which developed after three to five days, was apparently produced by an increase in the number of parietal cells and a reduction in the number of cells secreting pepsin. The concept that serotonin might play a major part in determining the rhythm of bowel movement in man was tested, with negative results, by demonstrating that the urinary output of 5-hydroxyindole acetic acid was not increased in various types of diarrhœa and that, although a banana diet produced a five-to-ten fold increase in serotonin excretion in healthy subjects, diarrhœa was never induced.[5]

In a history of the British Society of Gastroenterology

1. *Gut*, March, 1960. Articles may be sent to the Editorial Secretary, *Gut*, Central Middlesex Hospital, Park Royal, London, N.W.10. Subscriptions (£3 per annum, single number 17*s*. 6*d*.) may be sent to the Publishing Manager, British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1.
2. Doll, R., Swynnerton, B. F., Newell, A. C. *Gut*, 1960, **1**, 31.
3. Watkinson, G. *ibid*. p. 14.
4. Clarke, S. D., Neill, D. W., Welbourn, R. B. *ibid*. p. 36.
5. Connell, A. M., Rowlands, E. M., Wilcox, P. B. *ibid*. p. 44.

Dr. Thomas Hunt [6] says that publication of the new journal is justified both by the special interests of this specialty and by the size and authority of the society. The first issue helps to vindicate his claim.

PROPHYLAXIS OF RHEUMATIC FEVER

NOWADAYS most physicians dealing with rheumatic fever, especially in children, pay much attention to prophylaxis against streptococcal respiratory infections. This measure, applied continuously during the years of greatest susceptibility to recurrence after an attack, provides a high degree of protection against further cardiac damage. Much of the work on prophylaxis has been done in the U.S.A., where a high recurrence-rate in unprotected cases seems to be the rule.[7] In the United Kingdom recurrence-rates, though rather poorly documented, are apparently lower; but evidence has been forthcoming that here too prophylaxis is worth while,[8] and efforts have been made to overcome objections to it.[9] One of the main difficulties is in securing regular administration: continuous prophylaxis with oral penicillin or sulphonamide depends on a close understanding between family doctor, parents, and children. The difficulty of making sure that patients continue to take their tablets increases as the interval since their last rheumatic attack lengthens; and when recurrences do occur it is equally difficult to establish whether prophylaxis has in fact been omitted. Daily prophylaxis is usually regarded as more efficacious than administration of penicillin only for treatment of respiratory infections —although this method, properly and consistently used, can undoubtedly protect against recurrence.[10]

Lim and Wilson [11] in New York studied ambulatory rheumatic children attending a rheumatic clinic monthly for six years. One group of patients (group 1) received continuous oral penicillin prophylactically and were also treated with penicillin when respiratory infections occurred. Another group (group 2) received penicillin only for treatment of respiratory infections. In each group, treatment consisted of a full ten-day course of an oral preparation, started at the onset of symptoms. β-hæmolytic streptococci were isolated from the two groups with about the same frequency (the organisms were apparently not serologically grouped) and the incidence of upper respiratory infections was also similar. Likewise the recurrence-rates were not significantly different: the recurrence-rates per 1000 patient-months were 7·5 in group 1 and 4·6 in group 2 for cases in which the last attack had been recent, and 3·9 and 2·4 when the interval since the last attack had been longer. In two British series,[8 12] in which prophylaxis had been continuous, there was a smaller but still significant recurrence-rate (about a quarter of that reported by Lim and Wilson).

It may thus be argued that the risk of recurrence is no greater when penicillin therapy is confined to the treatment of respiratory infections than it is with full prophylaxis. But this has been shown to apply only where careful medical supervision minimises the hazard of infections remaining untreated. Continuous prophylaxis is surely at present the most generally effective protective measure against recurrences.

6. Hunt, T. *ibid.* p. 3.
7. Stollerman, G. H. *Amer. J. Med.* 1954, **17**, 757.
8. Bywaters, E. G. L., Thomas, G. T. *Brit. med. J.* 1958, ii, 350.
9. Bywaters, E. G. L., Hallidie-Smith, K. *ibid.* i, 1234.
10. Catanzaro, F. J., Stetson, C. A., Morris, A. J., Chamovitz, R., Rammelkamp, C. H., Stolzen, B. L., Perry, W. D. *Amer. J. Med.* 1954, **17**, 749.
11. Lim, W. N., Wilson, M. G. *New Engl. J. Med.* 1960, **262**, 321.
12. Sanderson, G., St. Hill, C. A., Chamberlain, E. N. *Brit. med. J.* March 26, 1960, p. 913.

MIGRAINE

MIGRAINE may be viewed narrowly as an episodic headache with features suggesting a vascular origin, or as a syndrome with more widespread bodily disturbances. What initiates either the vascular change in cranial arteries or the visceral dysfunction? Careful clinical studies can still be useful here; and Selby and Lance [1] have reviewed five hundred cases confirming many previous observations, some of which are well known.

In almost a quarter of their cases symptoms started before the age of 10 years. In 15% there was a family history of epilepsy, and in 38% one of allergy. 67% regarded emotional upsets as a clear precipitating factor. 18% had clouding or complete loss of consciousness during attacks. Such disturbances of consciousness, which usually are not apparently epileptic, may occur only for a limited time—perhaps during adolescence or at the menopause. In treatment the value of ergotamine tartrate was confirmed. Histamine as an intravenous infusion (not administered for slow graded "desensitisation") also proved valuable, though Selby and Lance wonder whether this acted primarily on soma or on psyche.

In considering the migraine syndrome we may be misled by too exclusive attention to the headache. Gastrointestinal disturbances and peripheral vasomotor symptoms occur; and abnormalities of fluid balance are not uncommon. These may be secondary to disturbances of neural control; but possibly the imbalance, the electrolyte changes which accompany it, or some associated endocrine abnormality plays a primary part in the attack.

PHÆOCHROMOCYTOMA OF THE URINARY BLADDER

PHÆOCHROMOCYTOMAS (chromaffin paragangliomas) may arise in any part of the scattered extra-adrenal chromaffin-tissue system, which is situated in the prevertebral tissues of the abdomen as well as in the adrenal gland itself. Mac Keith [2] collected 165 reported cases, of which 152 were of adrenal origin and 13 arose in the retroperitoneal tissues between the kidneys. The tumours, which are usually benign, may cause paroxysmal hypertension or the adrenal sympathetic syndrome, leading to death if the tumour is not removed; or they may have no hormonal effects.

Pugh et al.[3] have described 4 cases of phæochromocytoma of the urinary bladder; only 3 other such cases have been reported previously.[4–6] These 7 cases are of great clinical and pathological interest. All the patients were females, whereas adrenal phæochromocytomas occur with about equal frequency in the two sexes. The ages ranged from 16 to 74 years, though in at least 3 cases symptoms had remained undetected or latent for many years before the diagnosis was established.

The presenting symptoms may be due to the presence of a tumour in the bladder, or may be due to hormonal activity. 5 cases presented with hæmaturia, 6 with hypertension (paroxysmal in 2), and 3 with headache, tachycardia, or facial flushing; and in 1 case distension of the bladder with 100 ml. of water caused headache and a rise of blood-pressure. Operation usually caused a sudden

1. Selby, G., Lance, J. W. *J. Neurol. Neurosurg. Psychiat.* 1960, **23**, 23.
2. Mac Keith, R. *Brit. Heart J.* 1944, **6**, 1.
3. Pugh, R. C. B., Gresham, G. A., Mullaney, J. *J. Path. Bact.* 1960, **79**, 89.
4. Zimmerman, I. J., Biron, R. E., MacMahon, H. E. *New Engl. J. Med.* 1953, **249**, 25.
5. Rosenberg, L. M. *ibid.* 1957, **257**, 1212.
6. Farley, S. E., Smith, C. L. *J. Urol.* 1959, **81**, 130.

fall in blood-pressure. The symptoms regressed after removal of the tumours, except in 1 case where the blood-pressure rose. 5 patients are still alive. 1 died forty months after operation from a cerebral hæmorrhage, and 1 immediately after operation in circulatory failure owing to the hormonal effects of manipulating the tumour.

The tumours were found in all parts of the bladder, and their size and weight varied considerably. A striking feature of the gross specimens was the alteration in colour during fixation in formol-saline, accompanied sometimes by yellow-brown discoloration of the fixative itself. Pigmentation of this type is well known in adrenal phæochromocytomas, and is thought to be due to the formation of an adrenochrome from the adrenaline precursors in the tumour. The chromaffin reaction was elicited in only 2 cases, but this reaction is capricious and requires special and rapid fixation. An excess of noradrenaline was demonstrated in the tissue of 2 of the tumours. 6 were benign, and 1 was malignant with metastases. Metastases are the only reliable criterion of malignancy, because the tumour cells lie in the muscle coat of the bladder wall and even grow into the perivesical tissues, thus simulating infiltrative growth. Such an anatomical distribution supports the belief that the tumours arise from paraganglia related to the autonomic nerves of the bladder wall.

The analysis of these 7 cases suggests that diagnosis before operation should be possible in some two-thirds of the cases. Hæmaturia combined with the adrenal sympathetic syndrome is almost pathognomonic. Hæmaturia with hypertension, especially if paroxysmal, is suggestive. The effects of adrenergic-blocking agents, the estimation of the urinary catechol amines, and bioassay of the excised tumour will substantiate the diagnosis in most cases. Rosenberg draws attention to two features of vesical cases. First, the excretion of urinary catechol amines may not return to normal until about a month after the tumour has been removed, and a temporarily raised level in the immediate postoperative period should not be regarded as evidence of a second tumour or of metastatic spread (nevertheless, in the case of Farley and Smith [6] a polypoid tumour obscured the right ureteric orifice and at operation a second nodule of tumour tissue was found at the bifurcation of the hypogastric vessels). Secondly, Rosenberg induced a hypertensive attack in his patient by distending the bladder with fluid introduced through a urethral catheter.

ROGER BACON AND THE PHYSICIANS

WE do not know for certain the time or place of Roger Bacon's birth, or when he died; but probably he was born in Somerset, about 1214, and lived till he was over eighty. He is reputedly buried in Oxford, and it was in that city that he is likely to have carried out his most notable scientific investigations. That he invented spectacles, left the earliest recorded formula for gunpowder, and predicted the development of the aeroplane, are matters of fact. The myths which surrounded him even in his lifetime credited him with the creation of a brazen head which talked, and his contemporaries held him to be a necromancer. All these things apart, he was certainly a man of unusual scholastic attainments and was accomplished in Greek and Latin, Hebrew and Aramaic. It was not, however, his prowess in physics or chemistry, nor the prophetic gifts which enabled him to foresee, for instance, the steam-engine and the telescope, but Bacon's criticisms of the medical profession that Sir John Charles made the subject of his Gideon DeLaune lecture, delivered on April 20 before the Worshipful Society of Apothecaries.

There are, he pointed out, at least eight Baconian treatises associated with medicine. Four are concerned with the related questions of the preservation of youth, the retardation of old age, and the prolongation of life. Three more are mainly pharmaceutical treatises, and the eighth is the racy and—despite its title—the helpfully analytical book, On the Mistakes of Physicians. All are written in simple, easily flowing Latin, and abound in vivid phrases (*Mundo senescente senescunt homines*, ageing men in an ageing world: Bacon regarded old age as beginning when the prime of life was over, at about forty-five or fifty; and, like Shakespeare, he recognised phases in the period of declination, and speaks of three groups—the old, the elders, and the decrepit). None of the others can approach the *De Erroribus* in originality of thought, or pertinence of expression. But it is the production, as they all are, " of a man of singularly practical mind, who was not in practice and had . . . few opportunities of getting certitude by experience ": and it is based upon Galen's system of medicine, as modified by Avicenna and the Arabic physicians, and accepted without question. There is, then, little in the work which can be regarded, even remotely, as clinical. There are none of those bedside vignettes we find in the ancient writers, brief and sharply drawn in the case of Hippocrates, copious and discursive when Galen is in charge of the patient. Nor is it merely an indictment of, or a diatribe against, contemporary practitioners. Its significance lies in its constructive criticism of the system, then prevailing, of what we would now call Medical Education.

Bacon listed six principal impediments to those who studied medicine. Certain of them, Sir John remarked, are as relevant today as they were in the 13th century. The first was an ignorance of language, which denied to many readers the original text of their source books. A second was an ignorance among doctors of the drugs they used: they could not recognise them, accepted old preparations in place of newly compounded ones, and were put off with substitute or sophisticated remedies. Above all, they did not know what they cost. Another obstacle to progress was the time wasted in futile arguments, and in the discussion of ill-defined problems, to the neglect of practical study. Bacon's next complaint reflects his enthusiasm for astrology, and he held that through failure to enlist its assistance a physician would become unduly dependent on chance and good fortune. Neglect of another subject, alchemy, was the theme of the fifth protest, and the term alchemy included not only the infant science of chemistry but also the whole of botany and zoology. Finally, Bacon considered a number of real defects in our knowledge, detailing in particular a lack of precision in diagnosing disease and in classifying it, our ignorance of a specific cure for many conditions, and our inability to explain their causation. All these gaps, he argued, might be made good by investigation using experimental methods. And, though Bacon was, throughout his life, an important and influential advocate of such methods, nowhere else has he expressed himself more clearly than in the pregnant final sentence of *De Erroribus*: " Neither the voice of authority, nor the weight of reason and argument are as significant as experiment, for thence comes quiet to the mind."

Special Articles

HOLIDAY ADMISSIONS TO A GERIATRIC UNIT

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FROM time to time the geriatric service in the north of Glasgow is asked to admit chronic invalids to hospital temporarily so as to allow their relatives to go away on holiday. Most of these requests come from relatives who are successfully looking after an elderly person not in need of permanent hospital care. Other patients really need hospital care, and the relatives have reached a point where they cannot carry on without a rest, though they ask to have the patient back home again after their holiday.

The temporary admission of both groups of patients can greatly help the relatives, and can also offer the unit an opportunity for useful work. But while many patients benefit considerably from their stay in hospital, others react adversely to the change of environment. During the past year 46 patients were admitted as " holiday cases " to geriatric units in the north of Glasgow, and we describe here the conditions in which they were cared for at home and the benefits and hazards of their hospital admission.

THE PATIENTS

Of the 46 patients, 19 were men and 27 were women. 6 were under the age of sixty, of whom 4 had disseminated sclerosis. 14 were between eighty-one and ninety, and 3, all women, were over ninety. The average age of the men was sixty-nine and of the women eighty. Cerebrovascular degeneration and cardiovascular degeneration were the major diagnoses in half of the cases, and a third had other chronic neurological disorders, such as hemiplegia and parkinsonism. The other patients had as their major diagnosis arthritis, osteoporosis, carcinoma, and amputation of a leg or legs. Many patients had multiple degenerative disorders. 18 were incontinent of urine at home, and 14 were incontinent of fæces.

21 patients had not been treated in hospital for their present ailments. Few had been investigated or were receiving specific treatment. We investigated all patients when they came in for their holiday and established a diagnosis. For a third of the patients it was different from, or additional to, the diagnosis given before admission. Most of the patients were treated with drugs, and 20 also received physiotherapy, 10 occupational therapy, and 11 were supplied with appliances, such as walking-aids, hearing-aids, commodes, a rubber urine-bag, and a hernia belt. Several wheelchairs and callipers lying at home unused, or incorrectly used, were brought to hospital with the patient and were suitably modified. By these means we succeeded in improving the general health, the ambulation, and independence of 17 of the patients, who returned home happy with their stay and appreciably easier for their relatives to look after. The following case-history is typical of this group:

A man of 67 had been confined to bed for three years with a diagnosis of cancer of the kidney and diffuse secondaries in the testes and the brain. He was dull, demanding, and unwilling to help himself, and his wife was exhausted by caring for him. He appeared physically robust, had full movement of all limbs, and no neurological abnormality. One kidney had been removed for cancer five years ago, and two years later one testis was excised, but showed only chronic inflammatory changes. Our investigations revealed excellent function of the remaining kidney and no evidence of secondaries. At first the patient resented attempts at reassurance and rehabilitation, but when he left hospital three months later he was able to get out of bed unaided, wash himself, dress himself, feed himself, walk to the lavatory and climb one flight of stairs, much to his own satisfaction and to the indescribable relief of his wife.

Many other patients, however, needed little or no rehabilitation, or were unable to benefit from it. 15 of these spent a more or less uneventful time in hospital and returned home unchanged. Most of them found their hospital stay a pleasant enough interlude and said they would be happy to return another time.

Among the others were many whose stay was unfortunately complicated by intercurrent illnesses or accidents, or who deteriorated physically or mentally while in hospital.

Several patients contracted infections of the chest or urinary tract. Many were bewildered by their change of environment and became confused and agitated. Others grieved for absent relatives or felt rejected by them and became depressed. Some patients became incontinent of urine for the first time, and a few developed pressure-sores, notably one man of sixty-four with disseminated sclerosis. His wife had nursed him for seventeen years without a single break occurring in the skin, but he developed a sacral sore two days after his admission, which took several weeks to heal. A woman of sixty-nine fell and fractured the neck of her femur. She became bedfast and could not return home.

4 patients died during their stay in hospital, 2 died immediately after returning home, and 10 others were sent home appreciably worse than when they came in.

A woman of eighty-nine with parkinsonism, depression, and urinary incontinence became more incontinent and depressed in hospital, developed pressure-sores, and died five weeks after admission.

A man of sixty-four with right hemiplegia, aphasia, and amputation of both legs died one week after admission from coronary artery occlusion.

A man of seventy-six was severely demented, aggressive, and incontinent on admission, and the relatives were advised not to attempt to take him home again after their holiday. He was transferred to a long-stay ward where he died of pneumonia ten weeks after admission.

A woman of eighty-six had shown signs of progressive dementia for four years. She was aggressive and very confused in hospital, developed incontinence, pressure-sores, and terminal respiratory infection. She died ten weeks after admission.

A woman of ninety-three had been in bed at home for three years following a fall. She was unhappy in the ward and resented attempts at rehabilitation. She remained otherwise well in hospital for three weeks but died on the day after her return home.

A man of eighty-three who was confused and incontinent but ambulant at home became depressed and increasingly confused during a stay of one week in hospital. A small pressure-sore developed but began to heal. He died suddenly one week after returning home.

Of the 46 patients, 12 never returned home. 2 of these were placed in an eventide home as their relatives were no longer able to look after them. 6 were transferred to long-stay accommodation—1 to a mental hospital—and 4 died in hospital. Only 26 of the remaining 34 were sent back home as planned within one month, the rest remaining in hospital for up to three months. Sometimes the stay was prolonged because the patient was still learning to walk, or was in some other way continuing to benefit from active treatment. More often the delay was because the patient was being nursed over a complicating illness, or because

illness among the relatives prevented them from taking the patient back home. Several times we discouraged the return home of a patient when we were convinced that the nursing burden was too heavy for the relatives and could not be sustained.

In general the patients who fared worst were the very elderly, confused, and incontinent. 1 patient in 5 under the age of seventy-four deteriorated or died, against 1 in 3 over that age. The results were apparently better among the men than the women, but this was merely due to the higher proportion of younger patients among the men.

In assessing the results it must be remembered that many of these patients were going downhill at home, and some would have deteriorated or died even if they had not been admitted to hospital. Nevertheless we have little doubt that removal to hospital for these patients is attended by very real risks.

THE HOUSEHOLD

We visited all the patients at home both before and after their stay in hospital, and we interviewed the relatives caring for them. The needs of the invalids dominated the lives of these people. When we asked what they thought of the patients' temporary move to hospital we often received the answer " It was a godsend ". For 8 of them this was their first holiday in over five years, and fewer than half of them had had a break during the previous two years. Although a few were anxious about the elderly person left behind, almost all had immensely appreciated their holiday.

11 of the patients had been cared for at home for more than ten years and 17 for between five and ten years. 13 patients were wholly confined to bed, and 8 others were only able to sit up in a chair for an hour or two each day. A third of the patients had not been out of the house for more than five years. Only 16 of them could go to the lavatory by themselves, 11 needed help whenever they had to go, and the remaining 19 had to use a bedpan or commode.

Most of the homes were rather better than those of the ordinary admissions to our units. All but 7 of the families lived in houses of three or more apartments. On average there was one person to a room and three and a third people to a household. On the other hand no fewer than 18 of the households lacked bathrooms, 15 had no running hot water, and 7 of these patients were being cared for in houses with no inside lavatory.

THE RELATIVES

The relatives looking after these patients were mostly middle-aged women.

12 wives were looking after their husbands, but we had no cases of husbands caring for wives. 6 patients were looked after by their sister. 22 daughters were caring for parents, but no daughters-in-law. 1 son was looking after his father, and incidentally sacrificing his chance of marriage by doing so. 3 nieces and 1 family friend were looking after an old person because there was no-one else to do it, and they did not want the patient to end his days in an institution. 1 old person had a paid housekeeper doing the work.

The average age of these relatives was fifty-six. None was under thirty, 6 were between seventy and eighty years of age, and one woman of ninety-one was being looked after by her sister of eighty-two. Only 11 of these 46 people said they were in good health. The others were having medical attention for different ailments or for symptoms of physical and mental strain—notably fatigue, back strain, and nervousness.

What is it like to look after an ill old person at home? We restricted our questions to the care of the patients' excretory functions, the care of the skin, and the problem of leisure.

A third of the patients could go to the lavatory alone, and a quarter could go with help, but 19 could not go to the lavatory. In less than half the households were commodes, bedpans, and urinals used. 18 patients were incontinent of urine and 14 were incontinent of fæces. The common method of dealing with incontinence in bedfast patients was to tear up old sheets for draw-sheets and for wrapping between the patients' legs. These were washed and used again rather than destroyed. One or two ambulant incontinent patients spent their second childhood, like their first, wrapped in squares of turkish towelling.

We were impressed by how much more could have been done to help their relatives by advice on disposable incontinence pads (which we found in use in only one household), by greater provision of commodes, urinals, rubber sheets, and rubber urine-bags, all of which are readily available, and by the provision of a foul-laundry service.

As it was, a tremendous amount of extra laundering, often of the most unpleasant sort, fell to the relatives. They all insisted on washing the patients' soiled linen by hand themselves, and would not allow anyone else to handle it. For the incontinent patients there was a washing to be done at least once and sometimes twice a day, and some of the houses had no running hot water. A quarter of the households had washing machines, a quarter used a laundry, launderette, or public wash-house. In the others all the washing was done by hand—sometimes as many as 70 pieces a week.

The care of the skin was almost always done by washing the part, drying, powdering, and rubbing with spirit, petroleum jelly, or zinc and castor-oil cream. Only half of the families were helped by the district nurse, who gave a bed-bath once or, occasionally, two or three times a week, and who then attended to the skin. It is a tribute to the care of these relatives that only two patients had pressure-sores when admitted to hospital.

Many patients were confused and disoriented, liable to get out of bed and fall, to turn on the gas, or to endanger themselves in other ways, and this was a problem to the housewife who was afraid to leave the patient alone when she went out for shopping or leisure. Neighbours, friends, and other members of the family were sometimes able to help. The person looking after the patient usually managed to go out on only one evening a week. A quarter of them said that they never went out at all.

Only one family had a local-authority home-help, and two others had private domestic help. We concluded that the home-help service could do little to help these households, for the problem was seldom one of home management, but rather of nursing care.

The following cases illustrate the burden of care borne by relatives:

Two unmarried sisters looked after their mother of seventy-four who had been confined to bed for four-and-a-half years with multiple cerebral thrombosis and blindness. She was doubly incontinent and was nursed in skirts made out of flannelette and washed by hand daily. The daughters regretted allowing their mother going to hospital because she was unhappy there, and gave up their holiday to take her home. There she developed gangrene of both feet, but the daughters continued looking after her.

A woman of eighty-eight, blind, arthritic, and doubly incontinent, was looked after during the day by a married daughter who lived nearby, and at night by a second married daughter who had come every evening for eleven years to sleep in her mother's house.

DISCUSSION

This study illuminates one corner of the large problem of home care of elderly invalids. We saw only the minority

of patients whose relatives sought holiday relief. Many households in this group were labouring under difficulties that could have been eased by the fuller use of available facilities, which had been perhaps insufficiently made known to them. A possible solution might be an advisory service for relatives caring for the elderly at home, based on a consultative health-centre for the elderly.

Our principal task was to assess the value of temporary holiday admission, and here our impression is that this service is so necessary and so beneficial to the relatives that it should be provided by geriatric units. Such a service makes economic sense, for it helps the relatives to keep the patients out of hospital for eleven months of the year. But because of the attendant risks we make the following recommendations:

1. At the request of the general practitioner all patients should be visited in their own homes by the physician from the local geriatric unit some weeks before the proposed holiday. After assessing the circumstances he should advise the relatives on the probable outcome and, usually, should leave to them the decision whether or not to proceed with the arrangement. He should emphasise the poor prognosis in the very old and confused, and should mention that there is a definite mortality associated with the move.

2. In planning the patient's transfer to hospital the physician should be generous with time. It is best for the patient to be taken to hospital a week before the relatives go away. This enables them to make their holiday arrangements free from anxiety, and allows them to visit the patient in hospital before going away. They can also satisfy themselves that he has been left in good hands and is not grieving for them. In the same way the relatives should be allowed a week to settle down at home again before the patient returns. From the patient's point of view a very short stay in hospital causes disorganisation without achieving any real benefit and we think a stay of four weeks is suitable.

3. The physician should decide in advance the kind of ward suitable for the patient. If he thinks the patient needs investigation and rehabilitation, he will reserve a bed in his acute unit. But the elderly bedfast and confused patients will be better off in the quieter atmosphere of a long-stay ward. Some of our failures may have been caused by exposing unsuitable patients to the brisk activity of a rehabilitation unit because of shortage of beds in long-stay wards.

4. Some of the distress caused to patients by hospital admission could have been avoided by giving them more privacy. Many elderly patients, after being confined at home for a long time, are upset by contact with other old people, especially when some of these are harrowing cases of confusion and incontinence. This attitude was expressed to us by many relatives in such words as, "We quite understand that hospitals have to put everyone in together, but Mother is very easily upset by seeing other people suffering. Wouldn't it be possible for her to have a little privacy? We would be willing to pay for it." One cannot but sympathise with these people. The alternative is to send the patient to a nursing-home, but the cost is often prohibitive, and nursing-homes cannot provide facilities for investigation and rehabilitation, while they are often unprepared to accept some patients—e.g., the incontinent. There are no amenity beds in our geriatric service, but we believe that there is a demand for such beds.

We have stressed the dangers of temporary admission of old people to hospital, because these are perhaps insufficiently appreciated. But our own most vivid impression of the work has been our pleasure in giving most of these overworked households a period of real relief from their burden. We have had the additional satisfaction of making many bedfast patients ambulant once again and putting them on the path to independence. We feel that a service which has these benefits to offer should be made widely available to those who need it.

We wish to thank our colleagues Dr. J. C. Crorie, Dr. Aloysius Dunn, Dr. Nanette Nisbet and Dr. A. M. P. Thomson, under whose care many of these patients were admitted. We also thank Dr. W. F. Anderson for his advice and encouragement.

Symposium

GENETIC STUDIES IN GASTROENTEROLOGY

A SYMPOSIUM on the genetic approach to the study of gastrointestinal disease was held by the Gastroenterology Research Group on March 31 in New Orleans under the chairmanship of Dr. VICTOR A. MCKUSICK (Baltimore).

Dr. MCKUSICK said that analysis of genetic factors in the disorders of a given system showed that the disease-entities tended to fall into two classes: rarer conditions in which the genetic factor was relatively straightforward; and common disorders in which genetic and environmental factors collaborated and made the genetic analysis more complicated. The questions asked and the approaches to the answers tended to be different in the two categories. In the rarer disorders interest centred on the nature of the basic biochemical defect and on the formal genetics (precise mode of inheritance, gene frequency, mutation-rate, relative fertility). In the commoner disorders, the questions were: was there a significant genetic factor in the pathogenesis; and by what mechanism did genes determine susceptibility to the disorder? The purpose of the symposium was to illustrate methods rather than to cover exhaustively genetic factors in alimentary disease.

Hereditary Hyperbilirubinæmias

Dr. BARTON CHILDS (Baltimore) contrasted the clinical and chemical features of four types of hereditary hyperbilirubinæmia: the Dubin-Johnson syndrome (D.-J.), the Rotor syndrome (R), the Gilbert syndrome (G), and Crigler-Najjar (C.-N.) syndrome. Taking all cases of D.-J. in the literature, the sex-ratio was 4·36 males to 1 female. If the cases reported from military installations were excluded the ratio became 3·12 males to 1 female. But when the sex of affected sibs of patients was considered, the male-female ratio was nearly 1:1, though still slightly greater than 1. Parent-to-child transmission was observed and either parent seemingly may transmit the trait, although the numbers were small. In R, parent-child transmission also occurred, suggesting dominant inheritance. In G, a defect in glucuronide conjugation of bilirubin could be demonstrated in those individuals with higher serum-bilirubin, but not usually in those with levels of bilirubin less than 5 mg. per 100 ml. C.-N. was clearly inherited as an autosomal recessive. The relation between G and C.-N. might have any one of three bases: (1) the same gene in heterozygous and homozygous state, respectively; (2) different genes at difficult loci controlling different enzymes; and (3) alleles at the same locus.

Hæmochromatosis

Prof. MAURICE LAMY (Paris) described a family study of hæmochromatosis in which 3 cases of hæmochromatosis were found among brothers of 30 probands. Nearly all patients had a raised serum-iron level and a raised iron-saturation coefficient of siderophilin. Among 67 offspring of probands the means of plasma-iron concentration were essentially the same for males and females under 15 years of age and for females over the age of 15. Sons over the age of 15 showed an elevation of the mean value and appeared to comprise two groups, about half having an abnormality of iron metabolism. The experience was considered consistent with the hypothesis that hæmochromatosis was manifest in individuals heterozygous for one gene. Patients with juvenile hæmochromatosis,

especially those born of consanguineous matings, may be homozygotes. Of 30 patients, 10 could be considered as definitely alcoholic. Although alcoholism may hasten clinical decompensation, a more fundamental role was doubtful. The recessive hypothesis favoured by some workers was based on little more than the observation of multiple affected sibs and the failure to observe the disease in successive generations. Since mothers were likely to transmit the disease without manifesting it, since clinical expression occurred late in life, and since diabetes, heart-failure, and cirrhosis may be otherwise interpreted in the family history, the rarity of reported direct transmission was not surprising. Only 2 instances of consanguinity in parents of patients were discovered in the literature.

Cystic Fibrosis of the Pancreas

Dr. ARTHUR G. STEINBERG (Cleveland) said that two frequent misconceptions of clinicians were (1) that if truly genetic a disorder would by necessity occur in more than one member in most families studied; and (2) that a recessively inherited trait should occur in precisely 25% of the members of a large group of collected sibships. In connection with the first point he indicated that of 2-child families only 6% could be expected to show 2 offspring affected by a recessive trait and not until one reaches families of 7 children can a majority (56%) of them be expected to show more than one affected member. In connection with the second point he indicated how mode of ascertainment influenced the proportion of affected sibs observed. In 141 cystic-fibrosis sibships studied by Steinberg and his colleagues, 48·9% of offspring were affected. Corrected for mode of ascertainment the data were consistent with a recessive hypothesis. Steinberg found cystic fibrosis rare in Negroes and suspected that it was totally absent in pure Negroes. Two previous estimates of frequency of the disease (q^2) had been 1 in 600 and 1 in 1000 live births, giving a gene frequency (q) of 0·041 or 0·031 respectively. To maintain such a high gene frequency in the face of gene loss from death of homozygotes before reproduction, one could suggest either a mutation-rate of 1 in 300 or 1 in 500 genes per generation or a relative fertility advantage of the heterozygous carrier over the homozygous normal, estimated by q/p, or about 3%. That is, for each 97 offspring of a homozygous normal parent there should be 100 offspring of a heterozygous parent. In an intensive survey in Ohio Steinberg attempted total ascertainment of cases of cystic fibrosis among births between 1950 and 1953. Thereby, he arrived at an estimate of 1 in 2800 live births for frequency of the disease, 0·019 for gene frequency and 1 in 27 for frequency of heterozygotes. A fertility advantage of less than 2% would alone maintain the gene frequency. An impracticably large sample would be required to demonstrate such advantage. Cystic fibrosis was the most frequent genetically determined lethal disease of childhood.

Intestinal Polyposis

Dr. T. EDWARD REED (Ann Arbor) said there may be five different genetic varieties of intestinal polyposis: (1) classical familial polyposis of the colon, which in Michigan appeared to have a frequency of about 1 in 8000; (2) the Peutz-Jeghers syndrome (generalised intestinal polyposis with melanin spots of the oral mucosa, lips, and digits); (3) the Gardner syndrome (colonic polyposis associated with osseous and soft-tissue tumours); (4) the possible syndrome of Turcot-Deprés-St. Pierre (colonic polyposis and brain tumour); and (5) possibly single isolated polyps arising in families. The inheritance of the first three and the fifth was dominant. It was uncertain what the relationship was between Gardner's syndrome and classical polyposis. A large study in Michigan gave the following data in classical colonic polyposis:

Feature studied	*No. of cases providing information*	*Age of occurrence of feature studied*	
		Mean age (yr.)	*Range (yr.)*
First bowel complaints ..	32	28·0	5–57
Medical diagnosis of polyposis ..	66	30·2	5–58
Diagnosis of cancer	41	35·6	9–60
Death from cancer	29	38·9	9–70

Relative fertility of persons carrying the gene was estimated at 0·78. The indirect estimate of mutation-rate was 2 per 100,000 genes per generation. A possible linkage with the MN blood-groups had been described. Confirmation would be of theoretical and possible practical interest and might help to settle the question of the relationship of Gardner's syndrome to classical familial polyposis of the colon.

Hypertrophic Pyloric Stenosis of Infancy

Prof. BRIAN MACMAHON (Boston) reviewed familial aggregation in pyloric stenosis and suggested that an environmental influence might more adequately account for all observations than would be a genetic hypothesis. Specifically, he incriminated some feature of maternal handling. Earlier work had indicated in addition to increased occurrence in siblings of probands an impressive frequency in cousins—a finding not surprising for a common disorder (about 3 per 1000) such as this. Increased parental consanguinity, previously claimed, was doubtful and in such a common condition was not essential to a recessive genetic hypothesis. Some peculiar features of the familial aggregation were: (1) incidence was as high in half-sibs as in full sibs; (2) in affected parent-child combinations the mother was the affected parent more often than the father despite the preponderance of males in full series; (3) given an affected parent and child the risk to another child was 40%; (4) father-to-son transmission excluded sex-linked inheritance. In reports collected from the literature, monozygotic twins showed greater concordance than did dizygotic twins, but when a randomly selected series of twin births was investigated no difference in concordance could be demonstrated. Suggesting a postnatal origin consistent with environmental causation were the following points:

(1) The size of the tumour was related to the age of the infant at operation.

(2) In cases of two operations at brief intervals rapid growth of the tumour by the time of the second has been demonstrated.

(3) Association with birth-order suggested an environmental influence. The association with birth order was greater the older the patient at onset of symptoms. No association was demonstrable in cases with onset in the first weeks of life.

(4) Pyloric stenosis was about half as frequent in prematures as in full-term infants.

(5) The age of onset was earlier in infants born at home than those born in hospital.

(6) Onset was earlier in infants fed every three hours than in those fed four-hourly.

Duodenal Ulcer

Dr. D. A. P. EVANS (Liverpool) said that research on duodenal ulcer illustrated the way in which a genetic approach could contribute to the study of a common condition which seemed to be due to the interaction of hereditary and environmental influences.

Peptic ulcers had been shown to be twice as frequent among the living siblings of ulcer patients as in the general population. The relatives of duodenal-ulcer patients tended to have duodenal ulcers, whereas the relatives of gastric-ulcer patients tended to have gastric ulcers.

Specific genetic characters contributing to the inherited diathesis had recently been found. Series of duodenal-ulcer patients had more persons of blood-group O and more who were salivary ABH non-secretors, than did control series. These associations may be either causal or due to "stratification" within the population. The latter explanation seemed unlikely because the group-O association had been found in many different countries where the basic blood-group distributions were different. An experimental approach—namely, to find whether the associations held within sibships—had given as yet rather inconclusive results because insufficient sibships had been collected. The results did not suggest that the associations were absent within sibships.

Since there was a distinct possibility that these genetic characters were causal, certain physiological information was reviewed. There was a possibility that healthy group-O persons tend to produce more hydrochloric acid in the stomach than persons of group A. In this connection it was interesting to note that stomal ulcer was even more closely associated with group O than duodenal ulcer. What evidence there was tended to

suggest that quantitative factors in blood-group substance concentrations in body liquids were not responsible for the different susceptibilities of different phenotypes to duodenal ulcer.

From the biological point of view duodenal ulcer represented the selective effect of environment on a presumably balanced polymorphic system of eight phenotypes. By viewing ulcer in this way and studying the environmental influences acting on phenotypes of different susceptibilities, with and without ulcer, a clue may be obtained to the factors in the environment which cause duodenal ulcer.

Public Health

Foaming Waters

A NEW report [1] by the Standing Technical Committee on Synthetic Detergents, published last week, says that while there has been little change in the consumption of powdered detergents during the past two years the domestic use of liquid detergents has increased, and that foaming on rivers and canals and at sewage works continues to give rise to difficulties and complaints.

Detergent manufacturers agreed to supply the area of Luton and Harpenden with detergents based on an alternative alkyl benzene sulphonate from Aug. 1, 1958. From June that year, regular tests were carried out on sewage and effluent, and a continuing photographic record was kept of foam on the nearby river Lee. Unfortunately, it was not possible to replace more than about 70% of the synthetic detergent used in the area with detergents based on the new material. The experiment nevertheless shows that a greater proportion of the new than of the old material is removed during sewage treatment, and there has been less foam on the rivers. The report adds:

"The Luton experiment has confirmed that the new material is more completely oxidisable than the old. Part of the new material is destroyed quickly but a proportion of the remainder seems to be decomposed only slowly, and with some difficulty, so that even at Luton, where an effluent of exceptionally good quality is produced, sometimes at least a proportion of the new material leaves the works. It is reasonable to expect that where treatment is less complete than at Luton, removal of the new material is also likely to be less complete. Nevertheless, our tentative view is that the replacement of the old material by the new throughout the country would substantially diminish the troubles which have been caused by the increased use of synthetic detergents but it is as yet uncertain whether it will provide as complete an answer as we could have wished. Further research by the manufacturers is continuing, but meanwhile the general adoption of the new material in preference to the old would undoubtedly bring about an improvement."

World Health Statistics

The ninth annual statistical report [2] published by the World Health Organisation sets out the demographic and health conditions of the countries of the world in 1956. In the more highly developed countries mortality and the frequency of infectious diseases continue to decrease, but in other countries the increasingly complete statistical information now available reveals serious health problems.

In the first part of the report statistics of causes of death have been expanded. In the tables on causes of death figures have been given for deaths among young children by sex and by each year of age up to four years. A new table on the cause of infant mortality by age has been included. Other subjects which have been either expanded or newly introduced are cardiovascular diseases, malignant neoplasms, maternal mortality, and accidents according to the nature of injury. In the second part of the volume seasonal statistics of notifiable communicable diseases are given, with the distribution by sex and by age for certain of these diseases.

The third part relates to statistics of health personnel, hospital establishments, and vaccinations, and has also been rearranged and extended. The number of inhabitants of each country or territory per physician is also given; and the figures show vividly the still urgent need for medical personnel in certain areas of the world.

1. Third Progress Report of the Standing Technical Committee on Synthetic Detergents. H.M. Stationery Office. 1s. 6d.
2. *Annual Epidemiological and Vital Statistics*, 1956. Geneva: 1959. Pp. 705. £3. Bilingual edition (French and English). Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1.

In England Now

A Running Commentary by Peripatetic Correspondents

LIKE juke-box music, or the melo released at our local this week, or the latest poster for Muck (the anti-cancer cigarette), the annual panorama which the Royal Academy unfolds this week at Burlington House may not be Great Art; but, judging by past experience, it's what we, the public, want. And we want these various things for the same excellent reasons. The sickly intimacies of the echo-chamber, and the tough mixed-up guy at the cinema, and the cigarette-smoking off-duty Guards major are our beautifying mirrors: they reflect, just that bit more poignantly than we could, our numb tastes and aspirations; and they egg us on to put just that bit of extra effort into attaining their unattainable perfection. Even those rare birds who pride themselves on being different cannot ignore the common world around them: nor—unless they also happen to be provincial parvenus like Horace—would they wish to do so. But sadly I must report that that world at present is staunchly unheroic and aclinical. (The two always seem to go together: perhaps suffering engenders heroism, and heroism causes a great deal of suffering.) We, the art-loving public, in 1960 are prosperous, self-satisfied, physically fit, mentally vigorous, and spiritually dull. The reclining figures of Henry Moore have no belly and hardly a head. But Moore is an artist who is at least both frank and revealing. The lesser breed who clutter up the beautifully spacious galleries in Piccadilly paint a face in front of emptiness and wrap a waistcoat with a gold chain or an academic gown around nothing.

No crucifixion, no tortured saint, no battles, no road accidents: even the modern horrors of the rush-hour underworld look cosy in Jean Clark's "London Travellers". Only Royalty continue to suffer: perhaps the public, immune as it sees itself from all infirmities of the flesh, expects them to embody our common ailments as well as our moments of triumph. Over the years we have seen them chlorotic, hectically flushed, mildly myxœdematous, dyspeptic, anxiety-ridden, and endogenously depressed. But I would not venture to diagnose Epstein's last and rather disturbing offering.

To keep clinical interest alive, the less skilful painting creates its own weird and bloodless pathology. My own pet anomaly—happily prevalent among debs, duchesses, deans and bishops, headmasters, and chairmen of companies—is caruncolosis. It consists in a hypnotic prominence of the caruncule of the eyes; and its ætiology is satisfying in its simplicity. Or rather lack of simplicity. The real artist always simplifies—even at his most representational: he has learnt the simple truth that to render a three-dimensional world into two dimensions, and create movement from a piece of stone, he must simplify. The dabbler in portrait-painting is far too intent on copying what he thinks he knows must be there to leave anatomy well alone.

A single piece of sculpture redeems the display. Roy Noakes' "A Woman Reclining"—a wasted, contractured, helpless, hopeless, creature—is a geriatric problem all too familiar. It is also a wonderfully moving work of art, made with insight, passion, and compassion.

* * *

Now it can be told, says the *D——y M—l*, that during the televised mayhem which causes popeyed viewers to lace their nourishing bedtime cocoa heavily with barbiturates the sounds of fists and blunt instruments colliding with soft tissues is produced by men hitting grapefruits with wooden mallets.

It is high time that all TV afficionados said a big "Thank You!" to these dedicated craftsmen as, cramped in some obscure corner of the studio, they keep one eye on the fracas, one on the director, and one on the grapefruit in case someone tries to pinch it. (I know, I know, but unless you've got three eyes the job's impossible.)

These maestros of the mallet face unflinchingly risks and occupational hazards unique in industrial medicine. Apart from doing themselves harm by slipping about on the fruit-skins, they are prone to such traumatic conditions as mallet-

wielder's thumb, an acutely painful syndrome accompanied necessarily by acute retention of expletives.

Also grapefruit often explode on impact, with considerable fall-out; last year the contortions of a TV star who got some juice in his eye earned him an Oscar. Grapefruit percussor's psychosis is believed to be caused by the stemming of aggressive components of the Id during plays with excessive dialogue, and is liable, particularly after political telecasts, to abreact in frenzied episodes in which the patient propels grapefruit in all directions, so that the studio resembles the quarter-deck of Admiral Hornblower's flagship during a close action.

Yet today the grapefruit malleters' morale is high, for these men know they are no longer forgotten. Encouraged by Equity, the British Council has granted £5 million to help produce a semi-documentary feature, "The Ziz Zimmskliski Story", about the most-est grapefruit malleter of them all, whose career ended so tragically when he broke both wrists and his mallet on a grapefruit which had been kept overnight in the deep-freeze.

Production of this epic will start just as soon as somebody discovers how to make a noise like a mallet hitting a grapefruit.

* * *

"Boils" said the patient's mother. "Nothing but boils for months past, that's what we've had. First me mother-in-law, she lives with us, you know, she works at the hospital, she had a boil in her nose. Then Kim and me. Fifteen I've had, one after the other. And poor Kim—pulling her down, it is: goodness knows how many she's had. I went to the doctor and he said it was because I was run down. He gave me a tonic. Kim too. But the boils kept coming and he sent me to a skin specialist. He said we were getting them from the cats. He wanted us to get rid of the cats, but we couldn't do that, we couldn't really. Kim's so fond of them. But it's not that, is it, Doctor? It's a germ, surely it must be. It's one of these hospital germs, that's what I said to my mother-in-law. I've done some cleaning myself at the hospital only the doctor said I couldn't continue. I was so run down. It's one of these germs that they get in hospital, that's what I say it is."

Social pathology might be a promising new specialty.

Path. reports:

10215	Pus from one of Kim's boils	*Staph. aureus* type 80 resistant to penicillin and to the tetracycline drugs; sensitive to erythromycin and streptomycin.
10256	„ „ another of Kim's boils	
10612	„ „ yet „ „ „	
10665	Swab from Kim's nose	
10769	„ „ „ mother's nose	

* * *

A generous donor presented our children's ward with a fine chocolate Easter egg about the size of Humpty Dumpty. So on Sunday at the party, instead of the consultant beaming as Father Christmas, the houseman was given the destructive task of knocking the beautiful creation off the table on to the sheet-covered floor. Like the King's Horses, we failed to put it together again; but we had more excuse, for most of the pieces had disappeared.

* * *

The incidence of medical hagiography
Has a good deal to do with geography:
There are not many Eskimos in Guthrie's *History*,
But what Scotsmen are up to is less of a mystery.

* * *

In the book on child psychology it said that we should avoid making a child afraid of insects, and that a good way of doing this was to say "Hi, Mr. Bug!" in a friendly tone whenever one appeared. We tried this out, and it was very effective—so much so that at the height of summer we found our little girl holding the screen-door wide open and calling to the flies and mosquitoes, "Come in, Mr. Bug!" Which brings me to the point that

Medical psychology
Is different from medical entomology.
Psychology is about projection and cathexis,
But entomology is about infection and anaphylaxis.

Letters to the Editor

LEGAL ASPECTS OF HOMOGRAFTING

SIR,—Professor Woodruff (April 16) has done well to draw attention to the legal aspects of homografting. May I add some observations on bone-grafting in reparative surgery?

Homogenous bone has been used in this way for about half a century, but its widespread application came shortly after the late war when various methods of banking bone were introduced. The Royal National Orthopædic Hospital, for example, has had a bone-bank for ten years.

It has been shown repeatedly that homogenous bone is less suitable as grafting material then autogenous; however, it is not rejected by the body and provides a useful scaffold for the growth of bone from the host. There are circumstances in which bone homografts are indispensable, and for this reason efforts have been made to find the best method for preparing and storing this material. Recently some valuable work has been done at the Institute of Orthopædics by Dr. H. A. Sissons and his colleagues,[1 2] supported by a grant from the Medical Research Council. They made an experimental comparison of various types of stored homograft and found that freeze-dried bone sterilised by irradiation is a biologically acceptable material. The practical advantage of this method of preservation is, of course, that it permits the use of cadaveric bone, and places storage on a much less precarious footing. Hitherto, unreliable non-cadaveric sources have been almost obligatory—e.g., bone from suitable amputated limbs.

They then proceeded to prepare cadaveric bone for clinical trial, and similar work is already in progress in a number of other countries. Here, in Great Britain, surgeons from a number of other interested centres are anxious to meet to discuss standardisation of methods. It seemed to me that such a meeting should be held under the ægis of the Medical Research Council. But, for the present, it appears that this is not possible because the legality of removal of cadaveric tissues for clinical purposes has come into question. Like Professor Woodruff we are compelled to mark time, though we hope to arrange an informal conference so that when the way is clear it will be possible to go ahead without too much waste of time.

The Ministry of Health and the Medical Research Council are aware of the legal difficulties and no doubt some positive action will be taken before long. It is regrettable that apart from corneal grafting we are six years behind New Zealand, and it is in the interest of many patients that legislation to permit the removal of various tissues from the cadaver for surgical use should be promoted without delay.

The Institute of Orthopædics,
Royal National Orthopædic Hospital,
London, W.1. H. J. SEDDON.

SIR,—In his letter, Professor Woodruff gives an admirably balanced survey of the present place of homografting in surgery. My own interest is the management of terminal renal failure. I am sure that the renal homograft has a place in treating such cases. It offers a hope of relieving distressing symptoms and extending life, whilst involving no burden upon the patient by way of rigorous medical regime or abnormal mode of bodily function. The main theoretical problem is that of the homograft reaction, and the findings of my registrar, Mr. R. Y. Calne (Feb. 20) studying the effect

1. Chalmers, J., Sissons, H. A. *J. Bone Jt Surg.* 1959, **41B**, 209.
2. Chalmers, J., Lea, L., Stewart, L., Sissons, H. A. *in* Recent Research in Freezing and Drying (edited by A. S. Parkes and A. V. Smith). Oxford, 1960.

of 6-mercaptopurine on renal homografts in the experimental animal, have led us to believe that in cytotoxic drugs we have a means of controlling it, possibly more effective and infinitely more acceptable than by irradiation. Even so, I would not at this moment hold the homograft reaction as first among the practical problems involved, which are still considerable. Since Professor Woodruff has raised the legal aspects, I should like to support his plea for provisions to facilitate this work.

He also mentions appreciation of the situation by members of the public. Whilst still doubtful of the role of public education in medical matters that cannot readily be held to be other than of interest, I believe it to be of value in presenting a new concept in treatment, so that no distorted image should be formed in the public eye. This reminds us at once of the need for a most careful and sober presentation, especially of a subject that can easily be dramatised, and I warmly support Professor Woodruff's suggestion of a working party to consider appropriate recommendations.

The Royal Free Hospital, London, W.C.1. JOHN HOPEWELL.

HUMAN RELATIONS IN OBSTETRIC PRACTICE

SIR,—I am writing to express my delight at reading Prof. Norman Morris' views on this subject (April 23, p. 913). His article could not long last to fill a gap which has existed for years. As one who has worked as a midwife before working as a doctor, I have had many opportunities of seeing the "sausage machine" at work. The surprised and delighted look from a patient addressed by doctor or nursing staff by her name instead of "Mum" or "Mother" was enough to convince one of the need for a change of outlook.

The blame for what Professor Morris describes cannot simply be laid at the young doctor's and midwife's door. I have witnessed occasions where pupil midwives were severely scolded for "wasting time chattering with patients" when trying to reassure a crying young woman in labour. This point of view is still prevalent and changing far too slowly.

The interrelationships within the unit are another important point made by Professor Morris. I have seen many patients too frightened of sisters or nurses to address a doctor, let alone a consultant. I have also seen "uncooperative" patients being victimised—for instance, by giving them unnecessarily large amounts of aperients, causing sleepless nights, because the sister had them to give at her discretion. I remember an occasion when a patient had had so much that she needed a bedpan twelve times during a night, and yet receiving another dose in spite of her complaints.

With all due respect for Professor Morris' suggestions for reviewing procedure in clinics and wards, which will certainly do much to improve matters, something more fundamental is needed. As long as young doctors, midwives, and nurses are taught almost exclusively about the body, they cannot be expected to understand their patient's minds, with the rare exception of those saying and doing what is right through intuitive insight.

What is needed is extensive teaching of dynamic psychology as well as constant discussion of patients and their problems as practical examples to illustrate theoretical teaching. Meetings of medical and nursing staff as well as social workers would go far towards teaching all aspects of a case and its problems. Such teaching would have to start from the top. When I have had to refer neurotic or mentally disturbed patients for an examination, I have encountered more understanding and sympathy in young registrars than in consultants, who often cannot be bothered with frightened patients who hold up a busy clinic.

I should like to give an illustrative example from my own psychiatric practice.

Some years ago I saw a patient in an acute and severe anxiety state. She had not been well since the birth of her child five years previously. Her pregnancy had been planned and perfectly normal, and she had been delivered in a private ward of a London women's hospital. In spite of being a private patient she had had no attention beyond the most casual care. During her puerperium she was very severely depressed and slept little. The night nurse did not bother to report this, nor were her depression and general anxiety observed by anyone although she neither ate nor slept well. When she came home she had to fight infanticidal impulses for many months, and she never regained her mental health or ability to go back to a normal married life, until she had had a good deal of psychiatric treatment.

This woman would have been saved untold suffering if the staff had been trained to observe their patient's behaviour and if the woman consultant had not been completely preoccupied with the patient's tail-end. Whilst many doctors and nurses admit that there are emotional ups and down in the puerperium, they are often perfectly satisfied with making such a statement. They rarely go on to investigate individual cases, and give that assistance of which these patients are in dire need, even if their disturbance is not as severe as in the above example.

London, N.W.1. HILDA C. ABRAHAM.

RED-CELL REGULATORS

SIR,—The volume of publications on this topic in recent years is imposing and makes the reviewer's task a difficult one, but I feel there are several points in your leader of April 9 which should not be allowed to pass without comment.

The work of Reissman [1] and Erslev,[2] which gave the first clear demonstration of such humoral regulation, established that the response in the "recipient" animal was an increased production of normal red cells. It is clear, also, from the data of Borsook et al.[3] that their plasma extracts also evoked "normal" proliferation. Since that time intensive studies of the chemical properties of plasma and urine fractions capable of producing this response have shown that a non-dialysable mucoprotein may be derived from either source which fulfils the requirements of these earlier experiments.[4–7]

In the very interesting series of experiments by Linman et al. which you quote, evidence is forthcoming of a second factor influencing bone-marrow activity, which is thought to be non-protein, and ether-soluble.[8] Its effect on recipient rats is characterised by the production of *abnormal* red cells, microcytes with an apparently shortened survival, accompanied by reticulocytosis but no increase in hæmoglobin.[9] From their data it is apparent that this factor is demonstrable in conditions where there is hyperplasia of the marrow, including both primary and secondary polycythæmia, and also where there has been suppression of mitosis by X-irradiation [10] or by ^{32}P therapy in polycythæmia vera.[11] They conclude, perhaps somewhat hastily, that this factor is "not a by-product of hyperactive myeloid elements",[11] and that it is of ætiological importance in polycythæmia vera. However, an alternative hypothesis suggests itself—that it may be a factor formed in the normoblast in the premitotic phase stimulating D.N.A. synthesis, acting on other normoblasts if it should pass out of the cell, and that it might continue to be liberated by cells in which radiation

1. Reissman, K. R. *Blood*, 1950, **5**, 372.
2. Erslev, A. J. *ibid.* 1953, **8**, 349.
3. Borsook, H., Graybiel, A., Keighley, G., Windsor, E. *ibid.* 1954, **9**, 734.
4. Rambach, W. A., Alt, H. L., Cooper, J. A. D. *ibid.* 1957, **12**, 1101.
5. Gordon, A. S., Winkert, J. W., Dornfest, B. S., LoBue, J., Crusco, A. *in* The Kinetics of Cellular Proliferation; p. 332. London, 1959.
6. Jacobson, L. O., Goldwasser, E., Gurney, C. W. *ibid.* p. 344.
7. Borsook, H. *ibid.* p. 357.
8. Linman, J. W., Bethell, F. H., Long, M. J. *J. Lab. clin. Med.* 1958, **51**, 8.
9. Linman, J. W., Long, M. J. *Blood*, 1958, **13**, 226.
10. Linman, J. W., Bethell, F. H. *ibid.* 1957, **12**, 123.
11. Linman, J. W., Bethell, F. H., Long, M. J. *Ann. intern. Med.* 1959, **51**, 1003.

damage prevents the orderly synthesis of D.N.A. There is some evidence that humoral factors may be found in urine of patients with lymphatic reticuloses and chronic lymphatic and myeloid leukæmias which stimulate increased production of lymphocytes and polymorphs respectively [12] and these factors may be biologically analogous. Such a view of the origin of these factors is consistent with a neoplastic concept of these diseases.

There is an increasing body of evidence to suggest that the mucoprotein factor is the basic regulator of erythropoiesis. Erslev [13] has put forward evidence that the physiological regulator operates as a stimulus to differentiation in the "stem cell" rather than influencing rate of mitosis in later normoblasts and Alpen and Cranmore [14] have shown that the intermitotic interval of nucleated red cells in normal and anæmic dogs is the same. Alpen and Lajtha [15] have failed to show any acceleration of maturation or hæm synthesis in vitro in marrows incubated with a potent mucoprotein preparation of Van Dyke, whilst Gordon has shown a similar preparation to increase red-cell production in the isolated hind limb of the rat.[5] It seems likely, therefore, that this factor influences hæm synthesis only by the production of an increased number of early normoblasts, a view which Linman now accepts.[16] It is then to the mucoprotein factor that attention should be turned in polycythæmia vera, if the condition is believed to be caused by a disorder of physiological control, and here you misquote Linman et al.[11] After 14 days injection of extracts, increased red-cell and reticulocyte counts were observed, but *no* evidence is offered of increased hæmoglobin values in the recipient animals. In discussion they comment that "augmented amounts of the humoral agent which enhances hæmoglobin synthesis are also detectable" and the crux of the argument is the method used for assay of this agent. Their data are summarised below:

Korst et al.[17] described an assay method using rats in which mitosis had been partially suppressed by nitrogen mustard. In clinical assays they showed stimulation of iron utilisation by plasma from two cases of primary polycythæmia, but no stimulation by plasma from three cases of secondary polycythæmia. More recently [18], they reported a series of assays measuring iron utilisation in starved rats, and find that the *mean* iron uptake in rats treated with plasma from patients with both primary and secondary polycythæmia is greater than the mean of the control values, but do not state whether the difference was significant. The stimulation produced by these plasmas was considerably less than that produced by plasma from anæmic animals.

The former assay might be expected to respond to general stimulants of mitosis and possibly to certain nutrients for D.N.A. synthesis. The metabolic complexity of the fasted animal makes it difficult to evaluate minimal changes.

In our laboratory, we have used rats for assay which have been rendered polycythæmic by injected red cells—chosen because they might be expected to lack specifically the physiological stimulus to erythropoiesis. This preparation is responsive to whole plasma, and to mucoprotein concentrates from plasma and urine of anæmic subjects with both hyperplastic and hypoplastic marrow.[19] Stimulation of iron utilisation may be readily demonstrated following injection of plasma samples from patients with secondary polycythæmia but not with whole or greatly concentrated fractions of plasma from patients with polycythæmia rubra vera, thus casting grave doubt on the significance of findings mentioned above. Rimington and Nizet [20] have demonstrated yet another humoral agent in "anæmic" plasma which is ultrafilterable and active in vitro in stimulating hæmoglobin synthesis. Nakao et al.[21] present data which further delineate this from the mucoprotein factor, and this may also prove to be an intracellular normoblast metabolite or enzyme liberated into plasma; further findings in this field are awaited with interest. This factor may influence certain of the reported assays based on iron utilisation, but, as ultrafiltrates from highly "potent" plasmas are totally inactive in the polycythæmic animal, it seems unlikely that we are being misled by it.

We have confirmed the presence of the ether-soluble "erythrocytosis" factor in polycythæmia vera [19] and it seems reasonable to suppose that it plays some part with the other "lipid" factors [11] in producing the peripheral blood changes in polycythæmia (the microcytosis and possibly the mild white-cell and platelet elevations which often occur). However, caution should be exercised in accepting the view that changes in these factors are the primary cause of the polycythæmia.

Finally, since on present data both the mucoprotein factor [4] and the ether-soluble factor [8] may produce reticulocytosis in the normal animal, it seems unwise to grace with the term "erythropoietin assay" procedures based on this parameter alone. Osnes [22] demonstrated raised hæmoglobin values in his mice, but uses reticulocytosis alone in his routine experimental and clinical studies. The fact that Jones et al.[23] find lower values in renal venous than mixed venous blood in their cases of renal polycythæmia is in keeping with the view that they are predominantly demonstrating the lipid factor—the result rather than the cause of the polycythæmia. The slow return to normal values on assay after nephrectomy is again consistent with this interpretation.

Many American workers have applied the term "erythropoietin" to the mucoprotein factor,[6] the production of which appears to be intimately related to the kidney and it seems to be confusing to apply it now in a different context.

That reticulocytosis may be governed by other factors than those influencing erythropoiesis has been pointed out by Gordon [24] who showed that bicarbonate alone produced a reticulocytosis when injected into a hypophysectomised animal. One would like to see more than a 3% reticulocytosis produced by a plasma ultrafiltrate in an acidotic animal as clear evidence of a further independent renal erythropoietic factor.[22]

The London Hospital, E.1. D. G. PENINGTON.

PALLIATION IN MALIGNANT STRICTURE OF THE ŒSOPHAGUS

SIR,—The letter of Mr. Jamieson and others (April 23) seems to confirm our experience of the Mousseau-Barbin tube. We have met the following difficulties and complications in the use of that 'Neoplex' tube:

(1) The catheter portion is too soft for easy introduction; on the other hand, the use of a metal introducer makes the procedure rather dangerous. The only safe method seems to be a railroad one not unlike Mr. Moghissi's manœuvres.

(2) The lumen is too small and tends to block easily. We had a patient who drowned himself after drinking a cup of milk at the end of a meal consisting of semi-solid food.

(3) The tube rides up during the act of vomiting.

(4) The V-shaped funnel gives rise to an annular ulcer and to submucosal œdema above it—sometimes gross enough to cause complete dysphagia.

(5) Many patients were acutely aware of the presence of a foreign body in their œsophagus. In some the distress was worse than the preoperative symptoms. The lack of resilience of the tube and the shape of its funnel are the probable cause of this.

These points prompted us to devise a tube [25] that is more resilient, has a large lumen, carries a tulip-shaped funnel, can be stitched in position, and is in two parts that facilitate introduction under direct vision.

This tube has now been in use for over eighteen months. No ulceration or erosion has yet been met. Some senile patients tend to indulge in foods that may lead to temporary blockage of

12. Millar, F. R., Turner, D. L. *Amer. J. med. Sci.* 1943, **206**, 146.
13. Erslev, A. J. *Blood*, 1959, **14**, 386.
14. Alpen, E. L., Cranmore, D. *in* The Kinetics of Cellular Proliferation; p. 290. London, 1959.
15. Alpen, E. L., Lajtha, L. G. Quoted in ref. 14.
16. Linman, J. W. *in* The Kinetics of Cellular Proliferation; p. 359. London, 1959.
17. Korst, D. R., Bishop, R. C., Bethell, F. H. *J. Lab. clin. Med.* 1958, **52**, 365.
18. Korst, D. R., Whalley, B. E., Bethell, F. H. *ibid.* 1959, **54**, 916.
19. Penington, D. G. Unpublished observations.
20. Rimington, C. *Brit. med. J.* 1958, i, 1017.
21. Nakao, K., Takaku, F., Hiarashima, K. *Proc. Soc. exp. Biol., N.Y.* 1960, **103**, 47.
22. Osnes, S. *Brit. med. J.* 1959, ii, 650.
23. Jones, N. F., Payne, R. W., Hyde, R. D., Price, T. M. L. *Lancet*, Feb. 6, 1960, p. 299.
24. Gordon, A. S. *Physiol. Rev.* 1959, **39**, 1.
25. *Ann. R. Coll. Surg. Engl.* 1959, **25**, 165.

the tube—this is the exception rather than the rule. The œsophagus was transgressed in one of the intubations as a right pleural effusion followed the operation. No patient has as yet been troubled by retrosternal pain after intubation. Two patients with a broncho-œsophageal fistula have benefited from the operation. The tube has not been used in the treatment of benign strictures, but was used to relieve dysphagia in two patients with extraluminal tumours (bronchial and mammary mediastinal secondaries). The survival time ranged from two weeks to ten months. In all, 17 patients have been intubated. Biopsy confirmation was obtained in every case.

Hammersmith Hospital,
London, W.12. L. R. CELESTIN.

THROMBOPHLEBITIS FOLLOWING INTRAVENOUS INFUSION

SIR,—In your leader of April 23 you list as causes of thrombophlebitis following intravenous infusion (1) venous endothelium torn by needle point; (2) low pH of infusion fluid (doubtful); (3) duration of infusion (very important); (4) nature of tubing used. A possible addition is local sepsis or a coagulase-positive staphylococcus, or its exotoxin, in the infusion fluid.

You mention the work of Cruickshank et al.[1] who estimated the power of the unknown toxic substance released from tubing, by its effect on tissue cultures. You agree that the toxicity revealed by these tissue-culture tests is of clinical importance, but add that something equally effective but much simpler in technique is required for routine use.

I would like to suggest that the free-living forms in ordinary pond water could be used as test animals. Suitable short lengths of different varieties of rubber tubing could be firmly clipped, filled with suitable water, clipped again at the top, suspended overnight, and then the water from the interior of the clipped length of tubing allowed to flow into a watch-glass containing a selection of the active pond denizens. Their reactions can then be watched under the low power of the microscope.

This idea is not entirely original as will appear from a paper[2] on the mortality of aquatic insects and fishes caused by the use of latex tubing in experimental apparatus by J. W. DeWitt.

Pathology Department,
St. Margaret's Hospital,
Epping. FRANK MARSH.

MONDAY-TO-FRIDAY WARDS

SIR,—The hospital scene is constantly changing as new treatments and new drugs alter clinical needs. Over the past thirty years the fever hospitals have almost emptied; now the sanatoriums are gradually emptying; tomorrow, if present trends continue, it may even be the turn of the mental hospitals. But besides these medical changes the hospital must also face social changes.

Mr. Stallworthy (Jan. 9) has pointed out the fantastic costs of the hotel services which the hospitals are providing. At the start of the century people accepted the idea that hospitals were mainly for the homeless, friendless, or very poor. Those who were not in such need nursed their sick at home. Surgeons performed tonsillectomies on kitchen tables, mothers hung sheets soaked in carbolic lotion in front of the bedroom door of the child with measles. Yet this was before electricity, and often before W.C.s, came into the home. Modern conveniences, light, and space in council houses would make treatment at home a reasonable proposition for many patients, if it were supported by flying squads of doctors and nurses with adequate mobile equipment. What a saving of bills for food, service, heating, wear and tear of bedding, cleaning materials.

Another insidious change has been observed by those of us who have spent a working life-time in hospitals—the growing dearth of spinster nurses due to a high marriage-rate and the early age at which girls now marry. This will be felt even more acutely in a few years, as the old spinster sisters and matrons die or retire. If, as happened in Victorian times, it becomes the fashion for girls to marry at 17 or 18, there will soon not even be spinster student nurses.

Will the hospital of the future solve its problems by having some Monday-to-Friday wards? Obviously some patients will need inpatient care at the weekend, but would it be beyond the powers of clever organisers to arrange for the others—I would suggest as many as two-thirds—to spend the weekend at home? Will the day come when private cars and ambulances arrive at the hospital to take patients home at 5 P.M. on Fridays and return them at 9 A.M. on Mondays?

Rainworth, Notts. MARIE A. SIMPSON.

KEROSENE (PARAFFIN) POISONING

SIR,—The recent correspondence on poisoning by the ingestion or inhalation of domestic paraffin is of particular interest to those who practise in rural areas, since such poisoning constitutes a real, albeit diminishing, danger to small children. The higher standard of living of farm-workers and the increasing use of electricity in the country mean that less paraffin is used in the house, but it is used for various purposes on the farm, and some households still prefer it for its cheapness and are loth to part with their paraffin stoves. Unfortunately the oil companies have made it much more attractive of recent years by colouring it pink, blue, &c.

As one hazard shows signs of diminishing another appears to take its place and more recently the ingestion of furniture and floor polishes of various types has taken the place of paraffin poisoning as a cause of admission to the pædiatric wards in Lincolnshire. These substances are not thought of as dangerous in the average household and hence are not kept out of the way of young children.

It is surprising how often paraffin, and even petrol, are kept in bottles which have contained milk or soft drinks, or else in jam jars, and I now always inquire what kind of receptacle the paraffin was in. In one case a blue teapot containing paraffin was kept permanently on the hearth to revive the fire whenever necessary, and a child of 1 year 11 months who put her lips to the spout and drank an unknown quantity became so seriously ill that she was in a coma for five days. In a rapidly fatal case of petrol poisoning a child drank petrol from a jam jar on the floor of a garage while his father was carrying out repairs to the engine of his car within a few feet of the child.

I agree that the margin between the amount needed to produce unconsciousness and the amount required to kill is small, particularly as the victim is usually a child of less than 2 years. In a series of cases treated at Boston General Hospital between 1950 and 1955 the youngest was 1 year 2 months and the oldest 1 year 11 months.

On balance I think it is probably safer to wash out the stomach and risk a chemical pneumonia from inhalation. The alternative is coma, not unlike that of acute alcoholism, and gastrointestinal irritation. Nevertheless the chemical pneumonia produced by inhalation of paraffin or similar substances may take a very long time to resolve and does not always respond to antibiotics. Two of our cases still had demonstrable shadowing in the X-ray film of the chest after a month and another had a relapse of pneumonia 3 months from the date of poisoning. We have sometimes been surprised at the extent of the shadowing seen in the X-ray film compared with the paucity of physical signs on auscultation of the chest.

In the pædiatric service of South Lincolnshire Dr. Trevor Wright and I now regard the ingestion of paraffin or allied substances as a medical emergency requiring admission and energetic treatment. Experience shows that these chemicals are much more toxic than might be anticipated.

Boston General Hospital,
Boston, Lincs. I. M. CULLUM.

1. *J. clin. Path.* 1960, **13**, 42.
2. *Science*, 1957, **126**, 840.

EARLY TREATMENT OF STOVE-IN CHEST

SIR,—The wisdom of Mr. Barrett's advice (Feb. 6) on the management of severe chest injuries is the more pertinent because it underlines once again the vital need for surgeons of the widest experience if we are to do justice to the management of multiple injuries. Patients given adequate blood-transfusions seldom die from limb injuries, but they are often lost from respiratory embarrassment or damage to other vital organs, such as the brain and liver. It is surprising therefore that a general anæsthetic in the casualty department should be seriously advocated for the immediate treatment of a patient who amongst other injuries may have a flail chest.

It is a fundamental principle in the management of the critically injured that after a free airway and transfusion are established, repeated examination is the next priority, particularly in the assessment of brain and abdominal injuries. The administration of a general anæsthetic in a changing situation, frequently associated with injuries to the face, will daunt any but the most intrepid and carefree anæsthetist. The surgeon will be no less worried because of the possibility of other injuries.

That a tracheostomy and controlled respiration are lifesaving on these occasions is plain for all to see, but why not use local anæsthesia with the head and shoulders raised to relieve venous congestion? The patient will thus remain conscious and allow more mature assessment after control of his respiration.

Department of Surgery,
Alfred Hospital, Melbourne. EDWARD ALLCOCK.

PIPERAZINE ADIPATE IN HETEROPHYES HETEROPHYES AND OTHER HELMINTH INFECTIONS

SIR,—We found [1] that piperazine adipate and citrate were effective in *Heterophyes heterophyes* infections in divided doses of 12·6 g. and 14 g. respectively over 7 days. Larger trials were undertaken to confirm these findings. We studied the effect of piperazine adipate ('Nometan') in *Heterophyes heterophyes* infections in patients from the outpatient clinic of the rural health unit at Ezbet-El-Burg, near Damietta, an endemic focus of this infection.

Twenty patients were treated with piperazine adipate (0·3 g. tablets). Their ages ranged from 6 to 50 years and they were between 20 and 80 kg. in weight. The dose varied between 0·9 and 4·5 g. daily over a period of 2–10 days. The total dose ranged from 6·3 to 22·5 g.

EFFECT OF PIPERAZINE ON VARIOUS HELMINTH INFECTIONS

Infestation	No. of cases treated	Total dose of piperazine (g.)	Duration of treatment (days)	Cured cases
Heterophyes ..	20	6·3–22·5	2–10	11 (55%)
Ascaris	3	6·3–18	4–7	3 (100%)
Trichocephalus ..	2	6·3 & 12·6	7	2 (100%)
Trichostrongylus	1	21·3	6	1 (100%)
H. nana	1	18·9	7	0
Enterobius ..	1	18·9	7	1 (100%)
Ancylostoma ..	1	6·3	7	0

Eight of the twenty cases stopped passing ova after 4–5 days' treatment; and another three patients stopped passing ova after 6-7 days' treatment. The other nine patients continued to pass ova despite treatment.

Two patients infected with trichocephalus (one concurrently with heterophyes and the other with ancylostoma and ascaris) were treated with 12·6 g. and 6·3 g. respectively. In both cases stools were negative for trichocephalus, heterophyes, and ascaris but ancylostoma ova continued to be passed.

One patient who was infected with heterophyes and trichostrongylus took 21·3 g. of the drug over 6 days. After 3 days trichostrongylus eggs were no longer passed, but those of heterophyes were still passed in spite of the large dose given.

One patient infected with enterobius and *H. nana* concurrently with heterophyes received 18·9 g. over 7 days. Tests were negative for enterobius after 7 days, but the other eggs continued to be passed.

Side-effects of the drug were slight except in those taking more than 3·6 g. daily, in whom there was slight dizziness. The general condition of all patients improved: colicky pains subsided and appetite increased.

Follow-up stool examinations were done every other day for one month.

Department of Parasitology,
Faculty of Medicine, Ein-Shams University,
Cairo. H. F. NAGATY
H. M. KHALIL.

1. Nagaty, H. F., Rifaat, M. A., Salem, S. *Lancet*, 1955, ii, 827.

GENETIC TERMINOLOGY

SIR,—Professor Penrose (April 9) is perhaps unduly harsh in calling your terminology inaccurate. As regards "sib" or "sibling", it is the form you used, "sibling", which had the more precise and restricted meaning of "a relative" in Old English, and which is given in its scientific sense in the 1933 supplement of the Oxford English Dictionary. However, "sib" is shorter and gaining ground with geneticists.

As regards "monozygous" or "monozygotic", the difference appears to be between the present participle and the verbal adjective, which here has the meaning of the perfect passive participle. Since the fusion of germ cells precedes the twinning, "monozygotic" is more correct, and is given in the 1933 supplement. But it is an ill-sounding word, and "monozygous" is used in at least two recent textbooks. It would be nice to hear from a Greek scholar whether the frequent, but exact, use the Greeks made of the present participle could justify "monozygous".

Orpington. C. O. CARTER.

LUNG CANCER AND TOBACCO MOSAIC VIRUS

SIR,—I do not seem to have explained (March 26) clearly enough the assumptions that have to be made before the idea that tobacco mosaic virus (T.M.V.) is a cause of lung cancer (as proposed by Dr. Bothwell in his letters of March 19 and April 23) can be accepted. Lest silence should be interpreted as agreement with the new statement of the idea, I will try to be both brief and more explicit.

We may accept, for the sake of argument, the idea that specificity resides in nucleic acids; it has to reside in something and they are no less probable than any other type of molecule. In theory they offer superabundant possibilities for specificity; no two particles of nucleic acid that have so far appeared on Earth, if they have the complexity generally accepted, need have been identical. The idea that nucleic acids carry specificity, or in modern jargon "information", in the cell, pre-supposes that there is an immense number of different nucleic-acid structures or configurations in each cell. The observation that viruses maintain some continuity in their properties suggests that, if nucleic acid is the material controlling these properties, its constitution remains fairly constant. From these two propositions it follows that infection with T.M.V. adds little to the pre-existing complexity of the nucleic-acid pattern of the tobacco plant.

Only in exceptional or long-established virus infections—e.g., some warts—does the amount of anomalous nucleic acid in the infected cell approach the amount of normal nucleic acid. Most of the nucleic-acid breakdown products absorbed through the smoker's gut or lung will therefore be derived from normal tobacco nucleic acid rather than from T.M.V. Foodstuffs contribute still more "foreign" nucleic acid—often in a pyrolised state.

The idea that the breakdown products of virus nucleic acid are in some way special and more likely than those of any other

sort of nucleic acid to be carcinogenic is, on present evidence, simply alchemy. It depends on the old assumption that there must be chemical similarity between substances having analogous biological effects. Obviously the absence of evidence does not demonstrate that T.M.V. has nothing to do with lung cancer. My contention is only that the breakdown products of T.M.V. are no more likely to be involved than those of any other component of the tobacco leaf. I will go further, and suggest that there is no reason to think that, if people smoked hay, they too would not have an increased lung-cancer rate.

Rothamsted Experimental Station, Harpenden. N. W. PIRIE.

EFFECT OF BEER ON BLOOD FIBRINOLYTIC ACTIVITY

SIR,—The article of Jan. 23 by Dr. Fearnley and his colleagues is perhaps bad news, since it suggests we must now deny patients who are poor coronary risks this seemingly innocuous beverage.

The authors consider it is not the alcohol, but some substance produced during fermentation which reduces the blood fibrinolytic activity. As they used English draught beer, which is unpasteurised and only partially filtered, it is possible that this substance, whatever it is, may not be present in pasteurised and highly filtered bottled beer. All bottled beer is, I believe, pasteurised to prolong shelf-life, but it varies in gravity, colour, and lightness in different countries. Before concluding that *all* beer is potentially harmful in this regard would it not be interesting to test samples from some of the main beer-drinking countries of the world? I should be very glad, should Dr. Fearnley desire, to send him a quantity of pasteurised, double-filtered Canadian-bottled beer—strictly for experimental use, of course!

Mount Royal, Montreal. PETER H. NASH.

THE SHORTAGE OF NURSES

SIR,—There is a serious shortage of nurses in our hospitals. For this reason wards are closed. Some nurses are overstrained by their work and some have to take responsibility which ought to be carried by their seniors. In such a situation efficiency must suffer and an unregulated service develop. Not only is efficiency reduced but anomalies arise. Thus in some hospitals ward orderlies may receive, with overtime, a larger weekly salary (excluding superannuation) than the ward Sister herself.

But the nursing problem is not really a problem of money, though money can aggravate it and create a sense of injustice.

Many trained nurses are lost to the profession in Great Britain because they emigrate. More than 2500 nurses emigrated in 1958. If this is prompted by the adventurous spirit it should not be discouraged; but if it is the result of unsatisfactory conditions in this country a remedy should be sought without delay. In addition, many nurses are required for industrial undertakings; so that, although the total number of nurses has increased, the demands have increased also.

How can this state of affairs be remedied? Everybody must recognise that the care of the sick cannot take a second place. The first step should be a getting together of the various bodies concerned to consider what shortages actually exist and the possible ways of meeting them. It may be said that this is a task for the Ministry of Health alone; but this Ministry, although it may have the power, has, where possible, probably wisely preferred to rely on giving advice rather than on issuing orders.

In these circumstances a central body consisting of representatives of the Ministry of Health, the hospitals themselves, the British Medical Association, and the Royal College of Nursing seems to be the obvious means of attacking this national problem. If a new approach were made, pointing out the tremendous claim the sick have on our good will and the duty of the community to provide care and attention for them, the appeal should not be in vain. The time is specially advantageous for it because an increasing number of girls are and will be reaching school-leaving age and looking for worth-while careers.

This central body should be concerned not only with recruitment but also with amenities and accommodation for nurses and with incentives to take the less attractive posts. I should like to see a proportion of the annual budget for hospitals reserved for replacement or improvement of any nurses' accommodation which is substandard and needs upgrading. At present, such accommodation has to take its place in the queue, and its claim may have to give way to those of buildings obviously needed for the direct use of patients. Yet on the welfare of the nurses everything else in a hospital ultimately depends.

The present situation has continued far too long. If patients are to be properly cared for, it must be dealt with as an urgent matter.

Nottingham. S. ALAN S. MALKIN.

MOUNTAINEERS AND MEDICINE

SIR,—I shall certainly refer to Dr. Horniblow's interesting article of April 9 when next asked to advise a mountaineering or jungle expedition. Some things occur to me as worth adding.

There may be something to be said for two medical examinations: the first, of all potential members of an expedition far in advance of the departure date to look for conditions which would absolutely bar a man from going; and the second, of the final team (and any first " reserves ") much nearer the departure date to look for such things as upper respiratory tract infections and fungal infection of the feet. These may then be dealt with in preparation for the departure and, if need be, treatment continued on the way. While a chest radiograph is advisable, it should not be said that it will exclude bronchiectasis. Only a good bronchogram would do this, but this procedure need not be advised for all mountaineers! A careful history and clinical examination should suffice.

Dimethylphthalate (D.M.P.) is rarely mentioned in books and articles which call attention, sometimes in dramatic terms, to the discomfort of insect bites. It is cheap and easy to carry in the pocket and effectively abates attacks by many insects, thus reducing, at least to tolerable levels, skin irritation and infection. A newer and, it is claimed, better substance for this is diethyltoluamide.

Two pairs of properly fitting woollen socks and boots are to be recommended. An expedition's medical officer, however well he thinks he knows the expedition members, would be wise to inspect everyone's feet daily. There is a great temptation, after a long march, to wash the feet and then expose them and even to walk about barefoot. This should be forbidden. Insect bites and stings, thorns and cuts, apparently trivial at the time, are potentially very troublesome. Dr. Horniblow, having been to the Himalayas, does not mention that fearsome foot pest of Africa and South America, the chigoe flea (*Tunga penetrans*). The gravid female of the species burrows into skin of the feet and there swells with the multiplication of young. Early excision is the treatment and there are those who still insist that only the local inhabitants know how to do this properly.

The response of infected blisters to vitamin C is of interest. On the assumption that all members of an expedition are fit and have a full " reserve " of vitamins before they start, one

tends to advise against adding to the luggage by taking vitamins (sometimes to the chagrin of the expedition and its benefactors who tend to regard them as essential or at least as "pep" pills). Perhaps one should make an exception of vitamin C if the expedition is to be away for several weeks.

Most sore throats at high altitude are, I agree, probably due in the first place to the physical trauma of panting in cold dry air. One wonders whether lozenges, as often recommended, apart from the local anæsthetic action some of them may have, may not work simply by keeping the mouth shut!

Piles, especially painful external ones, can add greatly to the miseries of being at high altitude. The affliction is common enough to warrant taking an ointment for their specific treatment—especially one containing a local anæsthetic. This can be a great comfort too on raw surfaces from broken blisters.

A careful calculation should be made of what analgesics may be required. Headache is very common at high altitude and contributes much to the discomfort of fitful sleep. The demands for relief may be considerable, and woe betide a medical officer who soon runs out of aspirin!

London, S.W.14. HENRY BUNJÉ.

ORAL HYPOGLYCÆMIC AGENTS

SIR,—Your leading article [1] which compares tolbutamide and chlorpropamide in the oral treatment of diabetes mellitus reveals erroneous statements of fact and consequently arrives at amazingly false conclusions.

You state quite correctly that for all new agents "the standard of reference is insulin". Since in your words "the main criterion will be the relative toxicity" you should be aware of the serious toxic effects of chlorpropamide in the American experience.

The incidence of jaundice runs about 0·4% with 2 fatalities in 5000 patients according to the manufacturer's admission; others estimate this complication at 1%. In my own personal experience with over 3000 patients treated with tolbutamide I have never encountered a single instance of hepatic dysfunction let alone overt jaundice. On the other hand, 6 patients out of 400 treated by me with chlorpropamide developed serious disabling jaundice. Yet you state that chlorpropamide obstructive jaundice "seems to be less common than with tolbutamide". If the more than 500,000 patients now using tolbutamide in America were to be transferred to chlorpropamide then I would expect as many as 200 deaths in addition to thousands of instances of jaundice. In this city 2 patients succumbed recently to jaundice and bloody diarrhœa after three weeks of chlorpropamide (250 mg. daily). 1 of these patients died of this syndrome. Since the obstructive jaundice characteristic of chlorpropamide is, in the opinion of most liver pathologists, not related to dosage but to drug idiosyncrasy you can appreciate my anxiety about wider public use of this agent. The 2 cases I cited above reflect this lack of correlation to dosage.

The severity of hepatic toxicity and the appreciable side-effects of severe hypoglycæmia make it impossible for me to see any advantage of chlorpropamide over tolbutamide. In fact, since the American experience with tolbutamide is remarkably free from either hazard, in good conscience it should be preferred invariably to chlorpropamide. There can be no compromise with safety.

Mount Sinai Hospital, New York. HENRY DOLGER.

*** When we said "these seem to be less common than with tolbutamide," we were referring only to gastrointestinal disturbances, and we apologise for not making our meaning plain. Dr. Dolger seems to have been unfortunate in meeting 6 instances of serious jaundice among 400 patients treated with chlorpropamide. The incidence of jaundice recorded in the symposium published last year in the *Annals of the New York Academy of Science* was only a fraction of this. Hamff et al.[2] described 3 diabetics who developed jaundice during treatment with chlorpropamide, and after recovery 2 of them were given chlorpropamide again without ill effect, suggesting that the drug may not have been responsible in the first place. Others [3 4] have even claimed that chlorpropamide may protect against liver damage in man and rats; and Heinsen [5] noted recovery from severe jaundice when a diabetic was given chlorpropamide instead of insulin.—ED. L.

1. *Lancet*, 1959, ii, 1129.

BISALBUMINÆMIA

SIR,—We read with interest Professor Wieme's comments (April 9) on our paper on bisalbuminæmia. While his suggestion of a sickle-cell-trait analogy is intriguing, we would like to point out that in the sickle-cell trait, the proportion of abnormal hæmoglobin can vary between 22% and 45% of the total hæmoglobin, whereas in bisalbuminæmia the abnormal protein appears to regularly constitute about 50% of the total albumin.

Chemical Pathology Department, St. George's Hospital Medical School, London, S.W.1. GEOFFREY FRANGLEN.

AXILLARY LYMPH-NODES IN PATIENTS WITHOUT BREAST CARCINOMA

SIR,—Mr. McNair and Mr. Dudley showed, in your issue of April 2 that one-third of normal axillæ have palpable lymph-nodes, and they have thereby placed an item of common clinical experience on a sound statistical basis. They rightly deduce from this that the common method of staging breast cancer is inaccurate. I can go further and state that 50% of breast cancers are incorrectly staged, pathologically. To do so, I will first have to make four premises whose contained facts will not be disputed, though the exact percentages quoted may be open to discussion.

(1) In a series of breast cancers, about 40% present as Manchester stage I.

(2) As McNair and Dudley have shown, 33% of cases placed in stage II, are in fact stage I (false positive).

(3) Where lymph-nodes are clinically not palpable, they will in fact contain growth microscopically in 40% (false negative)[6]

(4) Wangensteen [7] states that 60% of patients in whom the axillary nodes are definitely involved will have occult or overt metastasis in supraclavicular or anterior mediastinal nodes, or both (thus placing them in Manchester stage IV).

Therefore, of every 100 cases of breast cancer, 40 will not have palpable nodes in the axilla. Of these, 16 (40%) will have microscopic metastases. Of the remaining 60, 10 will be stage IV, by virtue of distant metastases and cannot enter into the discussion. Of the 50 in stages II and III 17 (33%) will be incorrectly staged (false positive). Of the remaining 33, 20 (60%) will be too optimistically graded because they will have supraclavicular or anterior mediastinal metastases. To summarise:

100 cases:
- 40 stage I: *16* false negative; 24 genuine
- 50 stages II and III: *17* false positive; *20* false negative; 13 genuine
- 10 stage IV

Therefore a total of 53 cases have been incorrectly staged. This statistical juggling is pleasant mental

2. Hamff, L. H., Ferris, H. A., Evans, E. C., Whiteman, H. W. *Ann. N.Y. Acad. Sci.* 1959, **74**, 820.
3. Leevy, C. M., Tornow, A., Greenberg, P., Zinke, M. *ibid.* p. 725.
4. Knick, B. *ibid.* p. 858.
5. Heinsen, H. A. *ibid.* p. 709.
6. McWhirter, R. *Brit. J. Radiol.* 1955, **28**, 128.
7. Wangensteen, O. M. *Surg. Clin. N. Amer.* 1956, **36**, 1051.

exercise, but does the conclusion affect our comparisons between different treatment series, or even the prognosis in any given case? The answer is probably *no*, because all series contain the same errors in roughly the same proportions.

Leicester General Hospital. I. G. SCHRAIBMAN.

BRETYLIUM TOSYLATE IN THE TREATMENT OF HYPERTENSION

SIR,—Recent correspondence in your columns,[1–5] following the report from Hammersmith by Dollery et al.,[6] prompts us to comment on our experiences with the treatment of hypertension in an African hospital in East Africa.

Although the larger proportion of patients treated at our hypertension clinic present with hypertensive heart-failure, in approximately two-thirds of all patients the hypertension is due to chronic renal disease.[7 8] The mainstay of our treatment is ganglion-blocking therapy in the form of pempidine ('Perolysen'). We have also tried adrenergic blockers and so far we have treated 20 patients with bretylium tosylate ('Darenthin') and 25 patients with guanethidine ('Ismelin') for periods of up to four months.

Using bretylium, the Hammersmith workers found an unsatisfactory response in malignant hypertensives, in 5 of whom a daily dose of 2400–3600 mg. with added chlorothiazide proved ineffective. Overall, they obtained satisfactory response in 75% of their patients. Our experiences have been less encouraging, and in this respect we share the views expressed by Turner and Lowther.[1] Patients transferred from pempidine have felt greatly relieved of side-effects of ganglion-blockade at the expense of inadequate control of their blood-pressure. Tolerance has developed rapidly and it has not been unusual, in our patients, to reach a daily dose of 3000 mg. with added reserpine within a week of commencement of therapy without achieving adequate control of blood-pressure. Thus we have reverted to pempidine in resistant cases.

The following case illustrates extreme resistance to bretylium:

A 25-year-old Ganda male tradesman was admitted in hypertensive heart-failure of two weeks' duration. Blood-pressure was 200/160 mm. Hg. An additional complaint of painful micturition was found to be due to a chronic urethral stricture.

Investigations.—Hb 13·6 g. per 100 ml. Urine: moderate proteinuria, many red cells and pus cells in deposit. Urine concentration to 1010. Blood-urea 42 mg. per 100 ml. Intravenous pyelogram, poor excretion, no hydronephrosis. E.C.G. and X-ray of chest, compatible with gross left ventricular hypertrophy.

Treatment was begun with digoxin and hydroflumethiazide. Adequate blood-pressure control was effected with pempidine 10 mg. eight-hourly. Standing B.P. readings were 130–140/90–100. Because of persistent abdominal distension and early ileus, he was transferred to bretylium, starting with 200 mg. eight-hourly. Meanwhile he was also undergoing various stages of operative treatment for his urethral stricture under chemotherapeutic cover.

Resistance to bretylium was evident from the outset. Despite added reserpine and increases of the dose of bretylium, his blood-pressure remained in the region of 220/130. Four weeks later his daily dose of bretylium had reached 18·4 g. He felt profoundly weak. Blood-urea was 87 mg. per 100 ml. The standing B.P. was 170/150. His suprapubic cystotomy had become infected with *Pseudomonas pyocyanea*, coliforms and proteus. He was changed to guanethidine 25 mg. eight-hourly but no improvement was noted in his blood-pressure reading for the next three days. On the third day he died, presumably of severe urinary sepsis. Postmortem examination was refused.

Had he survived, it is possible that response to guanethidine would likewise have been unsatisfactory. He had not received oral diuretic agents latterly. We have now begun attempts with added chlorothiazide in all patients receiving bretylium and it is our preliminary impression that the combined regime is likely to be more satisfactory.

So far we have not recorded any major side-effects with bretylium except for postural giddiness in 2 patients. In none have we noted exertional hypotension as reported by Lowe and Rosenheim.[3]

We wish to endorse the view that greater care is required in the use of adrenergic blockers than with the established ganglion-blocking agents. Their action and fate, particularly in hypertension due to chronic renal disease, needs further observation and investigation.

Makerere College,
University College of East Africa,
Department of Medicine,
Kampala, Uganda. K. SOMERS.

1. Turner, R., Lowther, C. *Lancet*, 1960, i, 381.
2. Evanson, J. M., Sears, H. T. N. *ibid.* p. 544.
3. Lowe, R. D., Rosenheim, M. L. *ibid.* p. 655.
4. Fowler, P. B. S. *ibid.* p. 708.
5. Turner, R., Lowther, C. *ibid.* p. 769.
6. Dollery, C. T., Emslie-Smith, D., McMichael, J. *ibid.* p. 296.
7. Somers, K., Gitau, G. R. *S. Afr. med. J.* 1959, **33**, 515.
8. Somers, K., Gitau, G. R. In preparation.

MATERNAL INFLUENZA AND CONGENITAL DEFORMITIES

SIR,—Dr. Trimble (Jan. 9) points out that Dr. Coffey and Professor Jessop's findings [1] of an increase in congenital malformations in Dublin infants whose mothers suffered from influenza early in pregnancy is not in accord with the results in similar investigations in Iowa [2] and Los Angeles.[3] Although the case and control sampling in the American studies is by no means unassailable, Dr. Trimble suggests that the reason for the difference is to be found in the criteria for diagnosis in the Dublin investigation; these criteria were, he believes, inadequate. In making this inference he himself is committing an error.

If he were setting out to investigate the effects of virus infection during pregnancy on the young of a species of experimental animal, I am certain Dr. Trimble would take care to ensure that the genetic strain, the diet, the room temperature, and all the other variables in his controls were as similar as he could reasonably contrive to those in his experimental groups so that the groups would differ in only one respect—infection. In human work such control cannot be carried out, but it is part and parcel of modern epidemiological method to try to match control and experimental groups as closely as possible. Similarly when comparisons are made between two separate studies, whether experimental or epidemiological, the significance of any environmental factors should be borne in mind.

Setting aside the difference in rainfall, temperature, and hours of sunshine between Dublin on the one hand and Los Angeles [3] or Iowa [2] on the other, the fact that Ireland is a country perplexed by emigration, whereas in the United States—and particularly California—immigration is the chief concern, is germane to the present argument. The incidence of congenital abnormalities in Dublin (16 per 1000) is known to be high, and anencephaly in particular is a problem there.[4] Coffey and Jessop in their earlier investigations [4–6], have shown that malnutrition of the mother is associated with anencephaly and they conclude that low standards of nutrition may well be an ætiological factor in this condition—a conclusion which accords well with the careful clinical studies in Boston of Stuart, Burke, and their associates.[7–10] Coffey and Jessop in their latest paper have therefore reported the effect of an epidemic of influenza on a population whose standards of nutrition are low—in an earlier control group of 192 mothers

1. *Lancet*, 1959, ii, 935.
2. Walker, W. M., McKee, A. P. *Obst. Gynec.* 1959, **13**, 394.
3. Wilson, M. G., Heins, H. L., Imagawa, D. T., Adams, J. M. *J. Amer. med. Ass.* 1959, **171**, 638.
4. Coffey, V. P., Jessop, W. J. E. *Irish J. med. Sci.* 1955, **6**, 30.
5. Coffey, V. P., Jessop, W. J. E. *Brit. J. prev. soc. Med.* 1957, **11**, 174.
6. Coffey, V. P., Jessop, W. J. E. *Irish J. med. Sci.* 1958, **6**, 391.
7. Burke, B. S., Beal, V. A., Kirkwood, S. B., Stuart, H. C. *J. Nutr.* 1943, **26**, 569.
8. Burke, B. S., Harding, V. V., Stuart, H. C. *J. Pediat.* 1943, **23**, 506.
9. Burke, B. S., Stuart, H. C. *J. Amer. med. Ass.* 1948, **137**, 119.
10. Burke, B. S., Stevenson, S. S., Worcester, J., Stuart, H. C. *J. Nutr.* 1949, **38**, 453.

who had given birth to normal infants the total plasma-proteins were less than 5·5 g. in 28·4% of women, and the hæmoglobin under 70% in 24·5% of women.[5] Nothing is published of the living standards of the two groups of American mothers,[2 3] but it would be surprising if they were as low as those in the Dublin study.

Instead of suggesting that because the findings of the Dublin and American studies do not agree, one of them is *wrong*, Dr. Trimble might perhaps have considered whether Asian influenza is more likely to increase the incidence of congenital abnormalities in a poor underfed population than in a more prosperous one—and if so, why?

London School of Hygiene and Tropical Medicine, London, W.C.1. ROY M. ACHESON.

EXPIRED-AIR RESUSCITATION

SIR,—The report by Professor Woolmer and his colleagues (April 2) confirms the work that has been reported regarding the efficacy of an oral airway for performing direct artificial respiration (expired-air resuscitation).

It is not surprising that the untrained "rescuers" who performed resuscitation in the experiments described in your leading article had no difficulty in inserting a full-size anæsthetic-type airway, because their subjects were fully anæsthetised and paralysed for a surgical operation. However, such conditions do not usually exist in the field, and the casual rescuer may well have difficulty in his attempts to insert such an airway. Precious time may be lost if the jaw is tight, and even if the rescuer succeeds in placing the airway in the mouth, it might provoke retching and vomiting in a victim who may not be depressed to the level of unconsciousness where such reactions are abolished.

For these reasons, it is still essential to teach the casual rescuer, as well as professional first-aiders, the essentials of mouth-to-mouth and mouth-to-nose resuscitation—even if a manikin must be resorted to in order to avoid æsthetic objections during training. For those who are trained in resuscitation procedures, and for the casual rescuer who may need an airway (and who receives special training), I feel that the Brook airway (which has a shortened mouthpiece) fills the need best: it is relatively easy to insert, it provides a satisfactory air-passage, and it will not provoke retching or vomiting in a semiconscious victim, and the one moving part is a siliconed one-way valve which has an "infinite" shelf life. With the training programme previously described, most people can be taught this method of direct artificial respiration, which is highly efficient.[1–3]

Department of Anæsthesia, University Hospital, Saskatoon. ALLEN B. DOBKIN.

A PRACTICAL OXYHÆMOGLOBIN STANDARD

SIR,—Dr. Stallybrass (April 16) is right to remind us that the present-day international standard hæmoglobin corresponds to 14·6 g. per 100 ml. The difficulty however in day-to-day hæmoglobinometry is the lack of a practical standard solution by which to measure samples. With the almost universal use of oxyhæmoglobin in routine work, no adequate stable standard exists. The grey solutions sometimes used do not have the same absorption properties as oxyhæmoglobin and conditions may occur in which a grey solution produces a constant reading in a photo-electric colorimeter while a solution of oxyhæmoglobin will vary considerably.

An important contribution to this problem was made when Prof. E. J. King and Dr. I. D. P. Wootton, of the Postgraduate Medical School, undertook to provide laboratories at monthly intervals with a blood specimen chemically standardised for hæmoglobin content. This ensured that at least once a month it was possible to check the accuracy of our hæmoglobinometry. The demand for this valuable service has grown, and distribution of the specimens was later undertaken by Messrs. D. C. Keeler. The difficulty remains however that variations in apparatus occur unexpectedly, and in the absence of a reliable standard it may be some time before deviations are detected.

For the past year I have used a solution of hæmoglobin in 50% (v/v) glycerol as a standard. When checked at monthly intervals against the chemically standardised specimen supplied by Messrs. Keeler, it has proved remarkably constant, and no variation in its absorption spectrum has been observed in this time. Two strengths of hæmoglobin solution are made to correspond to about 14 g. and 7 g. per 100 ml., when read in the apparatus in use. A fresh blood specimen is lysed in 0·04% ammonia, and an equal volume of glycerol is added and thoroughly mixed. These stock solutions are kept at about −20°C and are removed from the refrigerator only to take a sample. The freezing-point of the solution is well below this temperature. For everyday use it is found convenient to keep samples of these solutions in standard cells or test-tubes normally used, and again these are returned to the refrigerator as soon as their readings have been checked. These solutions should not be left at room temperature for any length of time.

Paddington General Hospital, London, W.9. J. FIELDING.

RESISTANT TUBERCLE BACILLI

SIR,—Your leading article of March 12 on the subject of primary bacterial resistance is timely.

In Ghana, we have investigated the extent and pattern of bacterial resistance in 448 previously untreated cases of symptomatic pulmonary tuberculosis reporting for treatment at one centre in Ashanti during the period May to December, 1958, and have demonstrated resistance to streptomycin in 9·1%, to P.A.S. in 5·2%, and to isoniazid in 8·2%. Around 10% were resistant to one drug only and some 4·5% to two or three drugs. These figures represent a gross rise of 10% over the estimated level for 1957. The levels of resistance among new cases reporting for treatment and admitting previous chemotherapy elsewhere were: 37·6% resistant to streptomycin, 28·6% to isoniazid, and 5·0% to P.A.S.—resistance to two or three drugs being demonstrated in almost all resistant cases.

Chemotherapy, applied in the definitive sense, is known to be effective in the treatment of pulmonary tuberculosis provided drugs are applied in adequate dosage, in suitable combination, with constancy, and over a sufficiently prolonged period of time. The Tuberculosis Chemotherapy Centre, Madras, has laid down the minimum requirements for the success of domiciliary chemotherapy in a tropical urban centre, but almost none of these is available over wide areas of tropical Africa. The resistance figures for East and West Africa particularly underline what is likely to happen when definitive chemotherapy is applied under existing field conditions in underdeveloped territories. In Ashanti (and conditions there are similar to those in most other parts of West Africa) it is necessary to apply chemotherapy in the definitive sense, and it must be entirely ambulatory in the majority. At a practical level, therefore, the active treatment of pulmonary tuberculosis generally rests in the application of combinations of P.A.S. and isoniazid which, in view of the scattered nature of the population, must be taken without supervision. Recent work in West Africa has demonstrated that many do not take P.A.S. regularly (whether P.A.S. be dispensed separately from isoniazid or in the form of combined pills or cachets) and that the majority abscond during an early stage in treatment. Under conditions such as these, and considering that disease is usually extensive and often heavily cavitated, it is not surprising that high levels of bacterial resistance exist. It is certain that they will increase in the future as rapidly as they have in the

1. Dobkin, A. B. *Lancet*, 1959, ii, 662.
2. Dobkin, A. B. *Canad. med. Ass. J.* 1959, **81**, 458.
3. Brook, M., Brook, J. *ibid.* 1960, **82**, 245.

past unless urgent measures are introduced to rationalise management of the disease.

On the other hand, the matter of the clinical significance of bacterial resistance requires full investigation. Preferably such research as is required should be undertaken in Africa where the incidence of disease is high and where, from the available evidence, the resistance problem is most acute.

W. J. BELL
P. P. BROWN.

West African Council for Medical Research, Tuberculosis Research Unit, Accra.

THE PERSONAL DOCTOR

SIR,—Dr. Fox's review of medical care in the United States (April 2) has afforded me many insights. I find most of his argument on the functions of the personal doctor highly acceptable except in one respect: the health centre appears to me to provide some of the things necessary for the personal doctor's survival.

Dr. Fox mentions three ways in which health centres may contradict the ideal pursuit of personal doctoring:

(*a*) A specially designed building may detract from the homely relationship between doctor and patient.

(*b*) The use of ancillary workers (social workers, technicians, clerks, nurses) may interfere with the relationship between doctor and patient.

(*c*) Group facilities provide " heavy arms " for what should be a light mobile force in the battle for health.

But to deny the practitioner discussion with colleagues in general practice, adequate consulting-rooms, equipment, and ancillary help is perhaps to send him out altogether unarmed, and to deprive him of much that medical science has to offer. He surely needs to extend his diagnostic potential and to be economical with his time.

These requirements Dr. Fox implicitly concedes, and they seem to me to demand a centre. But he considers them less important than the personal relationship with which they may interfere. Yet he points out that " some doctors could make their patients feel like personal friends if they received them inside a refrigerator ". Extremes make good arguments, and this observation tells us that the quality of the personal relationship depends on something other than buildings and equipment. The extreme of this personal relationship is institutionalised in psychoanalysis, a case in which it is independent of such factors. Furthermore, many doctors working in association with each other or with social workers and nurses will testify that such groupings do not necessarily destroy the personal relationship. But it is certainly true that the increasing and inevitable specialisation in medicine is inimical to this relationship, except for the psychotherapist whose specialty it is.

The root of the personal relationship lies in the nature of the authority and responsibility which the doctor assumes with his patient (a conclusion which I must acknowledge I have reached by following through Dr. Fox's own arguments on professional freedom).

This responsibility is enshrined in the professional ethos of medicine, a set of rules essential to medical practice before the advent of technology in medicine. Without effective remedies, the doctor was obliged to rely for therapy largely on his interpretation of the natural history of an illness and the accommodation of this interpretation to the patient's psychological needs. He had to obtain a reliable history of symptoms, and complete confidence was necessary if the patient was to yield to anyone such intimate access to his life and body, and such extra-ordinary power over him. This was achieved through the set of rules embodied in the Hippocratic Oath. The obverse of this voluntary submission by the patient was the acceptance by the doctor of authority and full responsibility for the patient. Today some specialties may appear to have less need of this ethos, because attention is confined to a technical and restricted aspect of the patient's illness, and the social and psychological context of the illness can be ignored; in such a case responsibility usually rests elsewhere, depending on the particular organisation. This I think is part of the explanation for the lack of personal doctoring in specialties.

A main function of general practice is to maintain this traditional professional relationship—in other words, to offer the patient a single practitioner who will undertake full and continuing responsibility for him.

Such responsibility encourages the doctor to extend the boundary of medical care to whatever may concern the patient's health, and this therefore includes the social and psychological matrix of illness. Indeed, as Dr. Fox is concerned to show, the value of the professional relationship is largely in the psychological and social support which it offers the patient together with physical care—a combination which the patient can expect only from a practitioner who takes full responsibility for him in the traditional professional sense.

Dr. Fox shows that in the U.S.A. the basis of this personal relationship is being lost to medical practice. This is because with specialisation and large organisations goes a tendency to divided responsibility, the delegation of authority, and a chain of command. The doctor in the Family Health Demonstration at Montefiore delegates his authority in psychological and social matters to the psychiatric social worker and the health visitor and works in a *democratic* team. Once he does this he no longer has full responsibility, and the conditions for the full development of the personal relationship no longer exist.

For the practitioner to accept full and continuous professional responsibility (with the hospital as a specialist supporting service), he requires not only general clinical competence but competence in the social and psychological aspects of practice, so that the needs of the patient in his social context can be met. The home and family have to be seen, studied, and understood; and, if the practitioner is to hold this traditional area of medical practice, he will have to apply what psychology and sociology can teach to the so-called art of medicine.

To achieve psychological and social insights it is an advantage, even a necessity, to take the family as the basic unit of practice. Social and family problems cannot easily be brought into the scope of domiciliary care without the collaboration of medicosocial workers and home nurses. In addition, his function as family doctor would need to include the care of children, which in Britain is often the province of the clinic doctor, if not, as in the U.S.A., of the pædiatrician. This would be not only a step towards family practice, but one step towards achieving that unity of promotive, preventive, and curative work necessary to clinical competence. To incorporate into routine work preventive health examinations, screening techniques, and the maintenance of the chronic ambulant patient, modern clinical methods and technicians would be needed.

Thus in order to care for the whole family, in sickness and in health, the personal doctor would best take over and develop the personal services now given by local authorities, and he would have to be helped in this work by their ancillary workers. He would be the *leader* of a domiciliary team based on his practice. It seems to me that these are the minimal requirements which would enable the modern doctor to exercise the full and undivided professional responsibility that is fundamental to a personal relationship between doctor and patient.

Without these he risks becoming a psychotherapist or social worker of the second rank. Alternatively medical practice could abrogate this field and leave it to lay healers and priests, or psychologists and social workers, which latter is the implied solution of the Family Health Demonstration.

The development I have outlined could not take place without the kind of group organisation for which a health centre is designed. It would be uneconomical not to share these facilities.

It seems to me also that the view that the patient wants to attend a surgery that looks as much like a home as possible may be a projection, or an idealisation, of the 19th-century family doctor with a middle-class practice. But even if it is important, architectural guile is sufficient to solve this problem, as I think is well demonstrated in the Darbishire House Health Centre of Manchester University. To my eye, this looks more like a modest home than many private houses in some modern cities.

My argument, then, is that to achieve a personal relationship between doctor and patient, the crucial point is the distribution of professional authority and the form of administrative organisation. On this view the health centre is not a halfway house between specialist and personal doctor; it is an arrangement which allows the personal doctor to develop his utmost skill.

Department of Social and Preventive Medicine, University of Manchester. MERVYN SUSSER.

SIR,—There can be no doubt that personal practice (ex general practice) is the most important and most difficult specialty in medicine. Are we satisfied that the medical schools are giving as much attention to training in this specialty as they give to others? Can it be done without bringing some general practitioners into the hospital—for example, in charge of the casualty department?

One of your contributors suggests that *time* should only be spent on a patient when he is " really sick " and not when he or she is " bellyaching ", which presumably is a mental condition and not an abdominal one. Is it not the duty of any practitioner to try to cure the patient of this mental condition, which may in some cases be as crippling as a physical disease, instead of " speedily dismissing " him or her?

In my work I sometimes meet these " bellyachers " and hear their moans about their doctors. When talking to them I always try to be loyal to the profession, but in some cases there does seem to have been a " slip-up " on the part of the overworked doctor.

Oxford. MALCOLM DONALDSON.

HYPNOSIS AND UNREGISTERED PRACTITIONERS

Mr. PETER CASSON writes:

" Dr. Mason (Feb. 13) asks for information concerning harm done by hypnotists. His task is that of '. . . investigating the problem of *lay hypnotists* and the possible harmful effects which can be caused by the use of hypnosis by *unqualified practitioners* . . . great assistance to have available all the details of harmful effects which have followed the use of hypnosis by *unregistered practitioners* . . . of patients suffering from harm following the use of hypnosis by *unqualified practitioners* . . .' (my italics). Surely the investigation would be more scientifically oriented if Dr. Mason were to ask for information regarding anything adverse caused by *any* individuals using hypnosis? There is *no* ' qualification ' in hypnotism, either lay or medical, other than diplomas issued by various self-inaugurated societies, but this as a ' qualification ' is rather a homemade affair.

" Hypnotism is a psychological subject, not a medical one. Many of the major works on hypnosis are written by non-medically-qualified psychologists. The major research on hypnosis in this country is being carried out by non-medically-qualified psychologists. To me, Dr. Mason's proposal shows irrational bias, and I believe that his search will be unproductive.

" I, too, should be very interested to receive information about alleged harm done by hypnotism and I am sure that the fairmindedness of your readers would permit them to send me (at 17, Dorset Square, London, N.W.1) a copy of any information they send to Dr. Mason, for I am concerned with the correct application of hypnosis to medical and psychological problems.

" Please do not assume from the foregoing that I am anti-medical, far from it: my best friends are doctors and psychiatrists; I have trained quite a number in hypnosis; and all my patients with psychosomatic symptoms are vetted by their doctors before I treat them."

Obituary

HALLIDAY GIBSON SUTHERLAND

M.D. Edin.

Dr. Halliday Sutherland, who died in London on April 19 at the age of 77, was a versatile man. His experience, both inside and outside medicine, was varied and unusual, and with his natural talent for writing he used it to good effect in his reminiscences and in his books on social medicine.

The eldest son of Dr. J. F. Sutherland, a member of the Board of Control for Scotland, he was educated at Glasgow High School and Merchiston Castle School. After qualifying from the University of Edinburgh in 1906 he became an assistant in his uncle's practice in Spain, with some bull-fighting as a hazardous hobby. At Edinburgh, Sir Robert Philip had already aroused Sutherland's interest in diseases of the chest, and soon after his return to this country he became medical superintendent of the Westmoreland Sanatorium and later medical officer at the Marylebone tuberculosis dispensary. During the 1914–18 war he served as a temporary surgeon lieutenant in an armed merchant cruiser, and in the Royal Air Force. After the war he spent some fifteen years in general practice in Islington and later in Kensington, but he retained his interest in chest disease and also held part-time posts in that specialty.

Soon after the late war began he was appointed an assistant M.O.H. at Coventry and later he joined the mass-radiography centre at Birmingham, becoming director in 1948. He retired in 1951.

Throughout this full and active life he had found time for travelling and writing. One of his first books on his specialty was the *Control and Eradication of Tuberculosis*, which appeared in 1912. The *Arches of the Years*, published in 1933, described his life to the end of the 1914–18 war. Other books described journeys in Lapland, Scotland, Spain, and Ireland, and a lecture tour in Australia.

L. F. writes:

" Ever since his school and undergraduate days Sutherland had shown conspicuous literary ability, and it was no surprise to his friends that he achieved his major successes as an author. Blessed with a forceful personality, a puckish wit, and an insatiable appetite for adventure, he had also the rarer gift of communicating these qualities to paper. All his books contained entertaining material though none ever rivalled the first two pictureseque autobiographies (*The Arches of the Years* and *A Time to Keep*.) Halliday claimed to have been one of the few Englishmen, and probably the only member of the British Medical Association, to have played a bull in a

Spanish arena, and no-one who knew him could doubt it. His most bloodcurdling adventure, however, was in the 1914–18 war when, on reporting aboard ship, he was confronted by a worried first lieutenant who peremptorily instructed him to certify the captain insane, as he was giving orders which would sink the ship. Mimicry was one of Halliday's striking gifts and he was particularly admired for his uncanny skill in reproducing the foibles of his chief, Sir Robert Philip. It was sheer bad luck that his richest performance was given over the telephone, not as he thought to a fellow house-officer, but to the highly amused Sir Robert himself who loved to recite the story later.

"Controversy in speech and writing was the breath of Sutherland's life. He was eloquent and sincere but his perfervid Celtic spirit often impelled him far beyond his belief. After his conversion to the Catholic Church he devoted immense energy to upholding its medico-moral code, especially the prohibition of contraceptives. In his professional work he remained a devoted ally to Sir Robert Philip and rendered fine service in many departments of the great campaign against tuberculosis."

Dr. Sutherland married in 1920 Muriel, daughter of J. F. Fitzpatrick. They had one daughter and five sons, one of whom was killed in the late war.

Sir ARCHIBALD McINDOE

P. H. M.-B. writes:

"While supporting the tributes to the wonderful work which Archibald McIndoe has performed for plastic surgery and to his service for humanity, may I, as one of his former colleagues at the Hospital for Tropical Diseases, point out that he was elected surgeon to this hospital, then in Endsleigh Gardens, in 1932, and lecturer in tropical surgery at the London School of Hygiene and Tropical Medicine, posts which he held till 1939. These facts have escaped notice in his obituaries; yet it was here that he obtained an entry to surgical London, and facilities for beginning his work in plastic surgery."

Parliament

Limb-fitting Centres

IN the course of an adjournment debate on April 14 on the work of the British Limbless Ex-Servicemen's Association, Sir ROBERT CARY asked whether the work done at Roehampton could be decentralised by the creation of area limb-centres attached to the main orthopædic hospitals.

In her reply Miss EDITH PITT, parliamentary secretary to the Ministry of Health, said that a large artificial-limb and appliance centre needed about 20,000 sq. ft. and costs £100,000 to build. Centres had to be near bus stops, and there had to be plenty of space for ambulances and for testing patients on tricycles. Most of the Ministry of Pensions limb-centres started as part of its regional offices, and, except at Roehampton and Leeds, were originally office accommodation. The Ministry wanted to have them in hospitals, but as there were 21 centres of different sizes in England and Wales which did limb-fittings (and 9 others which did not) it would be costly to get them all in the right place—beside a hospital with an orthopædic department. They had to fit in with general hospital planning, and it was difficult to find really good sites for this specialised purpose. But where a centre had to be moved because it was inadequate they hoped in future to site it in or beside a hospital conveniently situated for the limbless which had an orthopædic department. A year or two ago the Wolverhampton centre had been moved to the New Cross Hospital. In Liverpool, they hoped to start building very soon at Mill Road Hospital, in Birmingham at Selly Oak Hospital, in Leicester at Leicester Royal Infirmary, and in Portsmouth at St. Mary's Hospital. Though they had not brought the limb service within the National Health Service, their aim was to bring the centres and the hospitals closer together.

Diary of the Week

MAY 1 TO 7

Monday, 2nd

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Prof. P. K. Duraiswami: Experimental Causation of Congenital Defects. (Hunterian lecture.)
UNIVERSITY OF LONDON
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. A. A. Liebow (Connecticut): Birth and Growth of Collateral Vessels.
POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. L. R. West: Echinococcosis.
WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hospital, W.2
5 P.M. Prof. A. St. G. Huggett: Fœtus as an Anaerobe—Some Prenatal Problems. (Almroth Wright lecture.)
UNIVERSITY OF BIRMINGHAM, Birmingham, 15
5 P.M. Prof. J. Z. Young: Mechanisms of Learning and Form Discrimination. (First of three William Withering lectures.)

Tuesday, 3rd

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Dr. J. R. B. Williams: Polymyositis.
UNIVERSITY OF LONDON
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Prof. E. Husted (Copenhagen): Ameloblastoma.
ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Prof. J. K. Russell: Megaloblastic Anæmia of Pregnancy.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. H. J. Wallace: Vascular Anomalies in the Lower Limbs.
INSTITUTE OF NEUROLOGY, The National Hospital, Queen Square, W.C.1
5.30 P.M. Prof. K. J. Zülch (Cologne): Recent Work on Cerebral and Spinal Infarction.
UNIVERSITY OF BIRMINGHAM
9 P.M. Professor Young: Mechanisms of Learning and Form Discrimination. (Second of three William Withering lectures.)

Wednesday, 4th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.15 P.M. *History of Medicine.* Dr. Cuthbert Dukes: London Medical Societies in the 18th Century. (Presidential address.)
8 P.M. *Surgery.* Mr. D. H. Patey, Mr. L. P. Le Quesne, Dr. C. G. Whiteside, Prof. A. G. R. Lowdon: Cholangiography.
ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5.15 P.M. Dr. W. V. McDermott, Jr. (Boston): Hepatic Coma.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. R. E. B. Hudson: The Human Pacemaker and its Pathology.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Fungi as Saprophytes and Pathogens.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. N. C. Oswald: Pulmonary Changes in the Reticuloses.
ASSURANCE MEDICAL SOCIETY
5 P.M. (11, Chandos Street, W.1.) Dr. F. Avery Jones: Prognosis in Alimentary Disease.
UNIVERSITY OF BIRMINGHAM
5 P.M. Professor Young: Mechanisms of Learning and Form Discrimination. (Last of three William Withering lectures.)
MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P.M. (18, Nicolson Street, Edinburgh.) Prof. G. W. A. Dick: Poliomyelitis.

Thursday, 5th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5.30 P.M. Sir Victor Negus: Air Conditioning in the Nose.
ROYAL SOCIETY OF MEDICINE
8 P.M. *Neurology.* Dr. W. H. McMenemey, Dr. Macdonald Critchley: History of Neurology.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Dr. H. T. Howat: Diagnosis and Treatment of Pancreatic Disease.
HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh.) Prof. P. R. Allison: Swallowing and Dysphagia.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Queen's College, Dundee.) Prof. T. Ferguson Rodger: The Neuropharmacological Approach to Psychiatry.
UNIVERSITY OF ABERDEEN
5 P.M. (Medical School, Foresterhill.) Prof. R. B. Welbourn: Hypophysectomy in Advanced Breast Cancer.

Friday, 6th

ROYAL SOCIETY OF MEDICINE
10.30 A.M. *Otology.* Dr. A. Glorig (Los Angeles): Air Marshal E. D. D. Dickson, Dr. Donald Stewart: Effects of Noise Upon Hearing.
3.20 P.M. *Laryngology.* Mr. H. D. Brown Kelly: Dysphagia in Adults (non-malignant), its Diagnosis and Management. Prof. Truls Leegard (Oslo): Management of Chemical Burns of the Œsophagus.
5.30 P.M. *Anæsthetics.* Mr. W. D. Tavernor: Anæsthetic Procedures in the Larger Domesticated Animals.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Dr. Deborah Doniach: Ancillary Diagnostic Methods in Thyroid Disease.
INSTITUTE OF NEUROLOGY
4.30 P.M. Dr. J. Purdon Martin: Observations on Muscular Rigidity and Its Relation to the Functions of the Basal Ganglia.
ROYAL COLLEGE OF SURGEONS OF EDINBURGH, Edinburgh, 8
3.30 P.M. Dr. A. Rae Gilchrist: The Cardiac Patient as a Surgical Problem.

Saturday, 7th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Faculty of Anæsthetists
10.30 A.M. Prof. E. A. Pask, Squadron-Leader J. Ernsting, Dr. J. B. Brierley, Dr. P. D. Bedford, Dr. B. R. J. Simpson: Hypoxia.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
NOON. Prof. S. Podvinic (Belgrade): Upper Respiratory Pathology in Asthma.

Notes and News

FREE MEDICAL CARE FOR THE ELDERLY IN THE UNITED STATES?

FROM A CORRESPONDENT IN NEW YORK

ONE of the key issues in the developing Presidential campaign is the Forand Bill, which would provide free hospital and other medical care for Social Security pensioners. More mail is now pouring into Washington on this subject than on any other legislative proposal, and both physicians and laymen are conducting pro and con campaigns which will have far-reaching effects on both national and State political campaigns.

The Bill, originally introduced in 1957 by Representative Aime J. Forand, a Democrat of Rhode Island, would provide up to 60 days' hospital care, 120 " nursing-home " care, and payment of surgical bills for Social Security pensioners aged 65 and over. It would be paid for by increasing the Social Security tax by ½%, with employer and employee paying a quarter each. With a rapidly increasing older population—now estimated as being over 15,000,000 in the 65-and-older category—the Bill has won tremendous support among the elderly and from many labour unions. On the other hand, it is being strongly opposed by organised medicine.

In a curious development, a plan advanced by Secretary of Health, Education, and Welfare Arthur S. Flemming was turned down by President Eisenhower. Flemming's plan was a subsidised system of voluntary health insurance for the aged. The Flemming plan encompassed private companies providing insurance covering the cost of hospital and nursing-home care, with the Federal Government sharing the major costs of the insurance premiums. Such insurance would be available to citizens at the age of 65 who had incomes of less than $4000.

Mr. Flemming was, in effect, left hanging on a limb. So were various Republican Party officials who realise how crucial the issue will be in the Fall elections. While Vice-President Richard Nixon, leading Republican Presidential candidate, is supposedly aligned with the Administration in opposition to the compulsory aspects of any insurance plan for the aged, Nixon is expected to come forward with an alternative plan in the near future.

Meanwhile, both the American Medical Association and the American Academy of General Practice are waging intensive war against the Forand Bill, while labour unions rally to support it. The battle is being fought in a setting in which voluntary health-insurance plans are in ferment throughout the country. The sharply rising costs of hospital care and drugs have impelled many Blue Cross groups, voluntary health-insurance plans, to ask for large increases in what their subscribers pay. These applications for higher rates have, in turn, caused many labour unions to protest and to threaten to set up their own health-insurance plans. Such threats have been raised both in New York City and in Detroit, while Blue Cross leaders have moved in the direction of one national Blue Cross organisation.

Illustrative of the heat of this controversy was a union rally of 6000 retired trade unionists in New York City to support the Forand Bill, in which President Eisenhower was sharply criticised for his opposition to the measure. Another sign of the keen feeling was the recent meeting in Philadelphia of the American Academy of General Practice, which urged its 26,000 physician members to send postcards and telegrams to Washington against the Bill.

MENTAL NURSING

ALMOST every paper that has been written about the changes that are being made in the care of mental patients show, either explicitly or implicitly, how much depends on the nurses. Not only are there more nurses than doctors, but nurses spend more time with each patient. In practice the patient must therefore depend on the nurse for much of the support and stimulus which help him to return to the community. By virtue of their own numbers and of the hours they work, the nurses are bound also to have an important influence on the atmosphere of the " therapeutic community " which is now part of the patient's active treatment. A committee of the Royal College of Nursing have been considering how the ward sister and charge nurse can meet these new responsibilities and opportunities.[1]

Many of their recommendations seek to ensure that the mental nurse should be consulted more freely, and kept more fully informed about policy in her own hospital; and that she should be represented on the nursing committees of the areas and regions. Another group of recommendations is concerned with opportunities for study and research. Promotion to ward sister and charge nurse should depend on willingness and ability to teach, and there should be a close link between classroom teaching and ward practice. The possibility of a shortened combined training for mental and mental-deficiency nurses is suggested. On the controversial question of an entrance examination to training the committee support an obligatory selection test.

Research in the care of long-stay patients and a critical review of traditional equipment and practice are other suggestions that will enable the nurse to find more satisfaction in her work and more time and energy to give her patients the modern treatment which so largely depends on old-fashioned kindness and sympathy.

HOSPITAL PLANS FOR WESSEX

ONLY a year after achieving full independence, the Wessex Regional Hospital Board last week gave a remarkably full account of how it means to develop its hospitals between now and 1972.[2] Having no medical school or teaching hospital within its boundaries, it has to provide some services which elsewhere are the responsibility of two separate boards.

Mr. S. V. Christie-Miller, chairman of the finance committee, estimates from Government statements that in this period a total of £532 million is likely to be available for hospital development in England and Wales; and he thinks that the Wessex board, with nearly 2 million people to look after, can hope for £24 million, of which £7 million may come out of its normal allocation while £17 million will go to schemes financed centrally by the Minister. Already it has had sanction for centrally financed schemes costing nearly £4 million. If the nation cannot live up to its economic expectations, the programme will remain the same but will take longer to complete; while if the Government are able to step up their capital investment in hospitals the work can be done sooner. The cost of the hospital service has come in for criticism in recent months, but " modern buildings mean less upkeep, lower costs, and better standards ".

Mr. P. G. Templeman, the chairman, spoke more specifically of delays in outpatient departments (caused by shortages of space and makeshift arrangements), the risks of sepsis, the obstacles to modern nursing and treatment, and the shortage of beds for mental defectives. The region has 115 hospitals with 17,400 beds, and the capital expenditure since 1948 has nearly all been on short-term remedies. Among the board's major aims, described by Prof. J. E. G. Raymont, chairman of the planning committee, are:

1. That each general hospital group should have an adequate main accident, orthopædic, casualty, and outpatient hospital.
2. That each outpatient hospital should have its supporting in-patient beds.
3. That each community should have a psychiatric outpatient clinic, short-stay unit, and day hospital within easy reach, and adequate medium-stay rehabilitation facilities. " We want to see our Mental Health services closely integrated with local health authority services, adequate occupational therapy buildings, and last, but by no means least, an end to overcrowding on the wards ".

Standards in operating-theatres are to be improved, and sterile articles are to be supplied to all hospitals from central sources. As chairman of the medical advisory committee, Mr. H. H. Langston also drew special attention to " the major emergency

1. A Comprehensive Mental Nursing Service—the Part of the Ward Sister and Charge Nurse. 1960. Obtainable from the college, 1a, Henrietta Place, London, W.1. Pp. 33. 2s. 6d.
2. Documents presented at a press conference on April 13. The board's address is Highcroft, Romsey Road, Winchester.

presented by the present-day accident", and the special problem of the ever-increasing accidents on the roads running through the Wessex region to the south and south-west.

The board's plans take the form of 17 major projects, which are set out with a timetable for their completion.

IMPERIAL CANCER RESEARCH FUND

THE Fund's new laboratories, now being built on the site of 44–46, Lincoln's Inn Fields, should be completed by the middle of next year. They are to cost at least a million pounds with another quarter of a million for their equipment; and the hon. treasurer's report, presented to the annual meeting on April 21, says that at least half a million pounds a year will be needed to maintain these buildings and the expanding team of scientific workers. Last year's expenditure was about £200,000.

In preparation for the expansion and reorganisation, ten new members of the staff have been appointed; and last October Dr. G. F. Marrian assumed full-time duties as director of research. The main subjects of investigation at Mill Hill and at Lincoln's Inn Fields are (1) the tumour-inducing properties of viruses, (2) the endocrinological aspects of cancer, (3) the leukæmias, and (4) the biological properties of tumour cells. At present the two first are absorbing the greater part of the research manpower, and one of the events of the year was the isolation by Dr. G. Negroni (from an Ak mouse with spontaneous leukæmia) of an agent resembling the polyoma virus studied by Gross, Stewart, and others in the United States. The report (obtainable from the Fund's office at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2) reproduces a remarkable electron photograph of a particle of this virus magnified 960,000 times.

A NEW INSTITUTE OF COMPARATIVE MEDICINE

THE Nuffield Foundation has made a grant of £100,000 to the Zoological Society of London to found an institute of comparative medicine, and to provide two senior research fellowships. The council of the society has asked that the name of Lord Nuffield should be associated with the name of the institute.

The society already has a modern animal hospital, and the institute will offer opportunity to increase knowledge of disease in animals, and thus serve the health of the society's collections. A committee of medical and veterinary specialists under the chairmanship of Sir Roy Cameron, with a planning group under the chairmanship of Prof. G. Payling Wright, has been appointed to advise the council on the organisation of the institute.

Mr. Richard Llewelyn Davies, director of the Nuffield Foundation division for architectural studies and professor elect of architecture in the University of London, will design the new building in accord with the overall plan for the gardens that has been devised by Sir Hugh Casson in collaboration with Mr. F. A. Stengelhofen, the society's resident architect. It is hoped that, in planning the institute, effect can be given to conclusions drawn from the study of laboratory designs for which the Foundation has been responsible over the past few years.

ILLNESS FROM COTTON DUST

BYSSINOSIS is still a serious problem in the Lancashire cotton industry. Dr. R. S. F. Schilling, who gave the Milroy lectures on this subject in 1956,[1] addressed the section of general practice of the Manchester Medical Society on March 28, when he said that in 1957–58, out of some 50,000 at risk, 68 cotton workers were recorded as dying of byssinosis and 448 received disability pensions. Investigations are in progress in this country, in Germany, and in Holland to discover the pharmacologically active constituent in the cotton dust causing the characteristic symptoms of chest tightness. As the immediate need is to reduce the dust, a combined clinical and environmental study has been made in Lancashire cotton mills[2] to determine safe levels of dust concentraton. At concentrations of less than 100 mg. per 100 cubic metres, no workers had symptoms of byssinosis, but at present it is not possible to achieve this level of dust control. The Shirley Device, which is a local exhaust ventilation system applied to the dusty points of a carding-engine, substantially reduces dust concentrations, and there is reason to hope that even in the dustiest mills concentrations of less than 250 mg. per c.m. can be achieved. This is the immediate target for dust suppression recommended to the industry. At concentrations between 100 and 250 mg. per c.m., 17 out of 250 workers at risk had persistent symptoms of byssinosis. Cardroom workers should therefore have regular medical examinations, so that those who are susceptible can be advised to leave their dusty environment before they are permanently disabled.

1. Schilling, R. S. F. *Lancet*, 1956, ii, 261, 319.
2. Roach, S. A., Schilling, R. S. F. *Brit. J. indust. med.*, 1960, **17**, 1.

NEW AMŒBICIDES

CLINICAL trials with some new synthetic amœbicides, which have been undertaken in the medical unit of the Hospital for Tropical Diseases, London, were reported last week by Dr. Stanley Bell, in a paper given to the Royal Society of Tropical Medicine and Hygiene.

The therapeutic efficacy of 'Entamide' (diloxanide) has previously been described, and the three new salts recently assessed are diloxanide benzoate, diloxanide piperazine sulphate, and diloxanide furoate. Of these the furoate has proved outstandingly successful, having an in-vitro activity 100 times as great as its parent substance diloxanide. The other salts are now principally of interest because of their differing absorbability from the gut while having similar in-vitro activity. The more absorbable piperazine sulphate has to date proved slightly more effective than the less absorbable benzoate.

Complementing the trials carried out in London, trials have been carried out in Nigeria by Dr. P. D. Marsden on the unit staff, and in these the efficacy of the furoate salt has been fully confirmed.

EXPIRED-AIR RESUSCITATION

As mentioned in our leading article of April 2, films have been made for showing first-aiders how to use the airways now recommended for direct artificial respiration. Dr. Allen B. Dobkin, of the University of Saskatchewan, whose paper on training with the Brook airway appeared last October (*Lancet*, 1959, ii, 662) tells us that the film *That They May Live*, and other training aids, can be seen by doctors in this country on application to Mr. C. N. Turner, Smith & Nephew Ltd., Welwyn Garden City, Herts. By arrangement with the University of Saskatchewan and Dr. M. Brook, the aids are obtainable from the Safety Supply Company of Toronto. The Brook airway is supplied in this country by W. H. Bailey & Sons, Ltd., 80, Bessborough Place, London, S.W.1. For copies of the film, application should be made to Dr. A. B. Dobkin, Department of Anæsthesia, University of Saskatchewan, Saskatoon, Canada.

University of Leeds

On Wednesday, May 11, at 3 P.M. at the General Infirmary at Leeds, Sir Howard Florey will give the Matthew Stewart lecture. He will speak on contributions of the electron microscope to the understanding of pathological processes.

University of Edinburgh

Colonel J. E. C. Robinson has been appointed part-time lecturer in the department of public health and social medicine.

North Middlesex Hospital

On April 26 Princess Margaret opened a new outpatient department at this hospital.

The department is housed in a four-storey block with a two-storey block on its north side. The chest clinic is on the lower ground floor. The patients' reception-room, records, appointment offices, urological department, five general-purpose clinics, dental treatment room and operating-theatre, outpatients' pharmacy, pathological laboratory, and X-ray department are on the ground floor. The department of physical medicine, which is on the first floor, has a hydrotherapy pool, three treatment rooms, gymnasiums, consulting-rooms, and examination cubicles, and an electrically screened room for electromyograph equipment. The main hospital pharmacy is on the first floor, together with a department for electrocardiography and clinical photography.

Royal College of Surgeons of England

The following diplomas have been granted jointly with the Royal College of Physicians:

D.A.—G. K. Stratford, R. J. B. Thomson.
D.L.O.—M. W. Brown.
D.P.M.—D. H. Miller.
D.I.H.—M. C. Narawane.
D.Phys.Med.—E. D. R. Campbell, Raymond Greenwood, P. N. Knight.
D.C.H.—Fadhil Khalil Abbousy, Israel Falke Abroms, Fadl Muhammed Abu-Laban, Soliman Husein Abu-Sittah, Patricia M. Akers, Jassim Mohammed Ali Al-Jawad, Jayant Shivabhai Amin, Asuquo Udo Antia, Bimla Arora, Audrey M. Ashworth, P. G. Atkinson, Jehangir Edalji Banatvala, Ivy Barua, Shirley A. Batten, Phyllis J. A. Bell, V. A. W. Blunt, J. R. F. Boger, M. D. Bowie, K. A. C. Brown, W. D. Bruce, W. L. Burland, Gwendolyn A. Burt, D. J. C. Cameron, Susan Campbell, Fook Kwee Chai, Tuck Kin Cham, Muthyala Chinna Pulliah Chetty, Gloria Cohen, Jean L. Cooper, Anna Cope, Gerald Corney, D. W. Davies, Patricia W. R. Daymond, Lalitha A. de Silva, Ponnahennedige Asoka Dias, Chandulal Sakerchand Doshi, A. E. J. Evans, D. R. L. Fernando, Elizabeth A. Fisher, Jacoba Geefhuysen, Mohamad Iqbal Ghayur, Patricia A. Girling, J. H. Goode, Bhola Nath Gupta, Margaret E. Happold, Razia Hasan, Naghat Hashmi, Joan M. C. Henderson, B. D. Hewitt, Marion E. Howard, Barbara H. Hutchinson-Smith, David Jacobson, Kanaya Harchandrai Jagasia, Elizabeth R. Jane, Mirza Agha Khan Javid, Cledwyn Watkin Jenkins, B. F. Johnson, R. P. Johnson, Shridhar Vinayak Joshi, J. D. Jowitt, Bishwa Nath Kapoor, H. B. Kean, Syed Usman Khaliq, J. B. Klaff, Parwati Shakuntala Limaye, Rhona Lindup, J. M. Littlewood, D. H. Livingston, Anne V. C. Lloyd, Shan-Shi Lo, Wan-Yee Lo, Tee Fun Loh, J. E. R. Lorimer, Maureen T. Lovett, Jane S. McFarlane, J. G. McHugh, Jean L. McNair, Ma Khin Ohn, Anne D. Micah, Raymond Million, Gillian A. Moody, Barbara A. Moss, D. S. Munro, C. H. Nourse, D. J. O'Connell, Margaret E. D. O'Flynn, Margaret M. R. O'Garra, Eileen T. O'Halloran, Bridget O'Keeffe, Mohamed Osman, K. R. Parker, Babubhai Mathurbhai Patel, Alina T. Piesowicz, Alice Shun-Haan Poon, Gwenllian J. Pryce, Mohammed Amin Radi, J. C. L. Rawes, David Redstone, J. D. Reid, M. E. Rivlin, G. A. Russell, Jayantilal Mohanlal Shah, Srinivasalu Naidu Shamanthakamani, Hafizulla Shariff, Mukteshwar Prasad Singh, Bishwambhar Dayal Sinha, R. P. Snaith, K. G. F. Somer, Gillian Strube, Myrtle E. Summerly, Anand Mohan Sur, Garden Hepburn Swapp, A. R. Taylor, Margaret Taylor, Marian A. Taylor, Prija Thanasuwat, Edith H. Thomas, Lesley F. Thomas, Eunice V. Turner, R. L. Walker, J. R. Wilson, I. G. Yule.
D.M.R.T.—Shu-Chen Huang, Kian Kang Rudy Khoo, Demetrios Laoutatzis, J. L. Lindsay, Komanduri Kutumba Narayanacharyulu, R. T. H. Shepherd, Ralph Shulman, V. E. R. Spence, P. F. Wale, Alison S. Wallace, G. C. J. Wiernik, T. S. Worthy, Ying Yeung Yeung.
D.M.R.D.—Theodore Chang, A. R. Chrispin, P. F. Claremont, A. L. Fletcher, Santi Pada Ganguly, Boris Golberg, E. H. Haynes, A. E. Hugh, Ivan Hyde, Aung Nyein, O. F. Paise, Ahmad Jerjees Shammaa, A. J. Slabber, D. P. Thomas, Vissarion Tzouliadis, E. H. Williams, J. E. Williams, S. M. Wolpert.
D.O.—Nisar Ahmad, J. H. Armstrong, T. C. Barras, Inderjit Singh Bhar, Golok Chandra Bhattacharjee, J. J. Blake, G. J. Bougher, Dorai Chamaraj, Hari Charan, J. A. Cox, E. W. G. Davies, H. J. A. Hahn, John Harrington, A. C. Hayes, Man Lin Hooi, Don Manupala Samarasekara Karunaratne, David Learmont, Mohamed Noor Bin Marahakim, F. O. Mueller, Myint Aung, Thimmanniah Channakeshaviah Nagaraja, M. C. Peteride, Padmakar Shrikrishna Pradhan, Gopal Nandan Prasad, W. E. Rees, Robert Renton, John Roberts, Kamal Mustafa Saleh, F. C. C. Schwerdt, Elkan Silverstone, Bhrigunath Singh, Dwarka Prasad Tiwari, P. G. Watson, D. J. Wilson.
D.T.M. & H.—Fawzi Tadros Abdel-Messih, R. M. Barnes, Gerald Bevan, R. S. Blewett, Hemraj Bodasing, D. E. Bradford, Narendra Kumar Chakravorty, Piti Changtrakul, Josephine Dobson, Nagendra Kumar Gami, Michael Gass, Ramachandra Eknath Godbole, Daniel Kelleher, Mohammad Aslam Khan, Houshang Khazrai, R. F. Knight, Stephen Leung Wing-Chiu, Adetokunbo Olumide Oluwole Lucas, Elizabeth M. MacCrone, Mary I. Malone, Khalid Rashid Minhas, Devendra Mohan, Abdol Baghi Nawab, H. G. Penman, Herbert Pullen, Abdul Majid Qureshi, Narasipur Srinivasa Iyengar Ramaswamy, Poul Erik Randrup, W. M. Robinson, Zafar Ali Sapru, Izzaldin Abbas Shikara, Khin Maung Tin, Margaret Tu, J. R. Wilson, William Young, Ahmad Junaid Yusuf, W. L. Zike.

Royal College of Physicians of Edinburgh

On Wednesday, May 25, Mr. F. John Gillingham will give the Morison lecture. He will speak on stereotactic surgery of the brain. On Wednesday, June 8, Prof. Robert Cruickshank will give the Lister fellowship lecture. His subject will be measurements in medicine. Both the lectures will be given at 5 P.M. at the college, 9, Queen Street, Edinburgh, 2.

British Society for Immunology

A meeting of this society will be held at the London Hospital Medical College, Ashfield Street, E.1, on Friday and Saturday, May 20 and 21. The meeting will include a symposium on immunological aspects of diseases of connective tissue. Further particulars may be had from Dr. R. G. White, bacteriology department, London Hospital.

Reciprocal Social Security with Germany

Reciprocal agreements on social security with Germany were signed on April 20. They cover all the benefits provided by the United Kingdom schemes of national insurance, industrial injuries insurance, and family allowances and the corresponding benefits in the Federal Republic of Germany and in Western Berlin. The agreements will not come into force until they have been ratified.

Institute of Hospital Administrators

The annual conference of this institute will be held at Scarborough from May 5 to 7. Sir Charles Morris will open the conference, and the programme will include a paper by Dr. R. F. L. Logan on assessment of future hospital needs.

Cell, Chromosome, and Virus Microscopy

A lecture and demonstration on the use of microscopy in cancer research is to be given at the Royal College of Surgeons of England, Lincoln's Inn Field, London, W.C.2, at 5.45 P.M. on Tuesday, May 10.

The speakers will include Prof. G. J. Cunningham, Prof. P. C. Koller, Dr. R. J. C. Harris, Dr. E. J. Ambrose, Mr. M. S. C. Birbeck, Dr. C. M. Clarke, Dr. A. J. S. Davies, Dr. S. H. Revell, and Dr. E. M. F. Roe. A new system of colour television will be used and the programme has been devised and coordinated by Prof. Alexander Haddow and Professor Cunningham. The college is arranging for medical students to see the lecture at 3.30 P.M. on the same day. Tickets for both meetings may be had from Mr. W. F. Davis at the college.

The Yorkshire Society of Anæsthetists will hold a meeting on Saturday, May 21, at 10.45 A.M., at Huddersfield Royal Infirmary. The speakers will include Dr. C. S. Ward, Dr. A. R. Kerr, and Dr. G. Jackson Rees.

The National Old People's Welfare Council have published a revised edition of their booklet on the organisation of a visiting service by an old people's welfare committee. In an appendix it describes some schemes which have been started in country parishes and in towns, in Wales, the North, and the Midlands, and offers helpful points drawn from this varied practical experience. Copies (1*s.* and 4*d.* postage) may be had from the Council, 26, Bedford Square, London, W.C.1.

CORRIGENDUM: *Placenta Prævia.*—The first sentence of Mr. Theobald's letter last week should have ended "sine HP", meaning without hypertension and proteinuria—i.e., without toxæmia.

Appointments

COOK, A. M., M.B. Aberd., D.P.M.: psychiatrist (S.H.M.O.), Stratheden Hospital, near Cupar, Fife.
HARRIS, RUTH F., M.B. Lond., D.C.H.: senior registrar, department of clinical neurophysiology, The Hospital for Sick Children, Great Ormond Street, London.
HENDRY, R. G., M.B. St. And., D.OBST., D.P.H.: senior M.O., Hertford.
JACKSON, J. W., M.CH. Dubl., F.R.C.S.: consultant thoracic surgeon, Royal National Orthopædic Hospital, London.
MILLER, HAROLD, M.D. Lond., M.R.C.P.: consultant pathologist, Portsmouth and Isle of Wight area pathological service.
PAPATHEOPHILOU, RITSA, M.D. Athens: senior registrar, department of clinical neurophysiology, The Hospital for Sick Children, Great Ormond Street, London.
PHILLIPS, D. E., M.R.C.S.: assistant M.O., Liverpool.
ROBERTS, H. E., B.M. Oxon.: M.O., Sheffield regional blood-transfusion centre.
THOMAS, H. M., M.B. Lpool, D.P.H., D.C.H.: M.O.H. and divisional M.O., Alderley Edge, Cheadle and Gatley, and Wilmslow, Cheshire.
WILSON, D. L., M.B. Glasg., D.T.M. & H.: assistant M.O.H. and school M.O., Carlisle.
WOOD, K. F., M.B. Leeds, F.R.C.S.: part-time consultant general surgeon, Leicester General Hospital and associated hospitals.

East Anglian Regional Hospital Board:

ATHLEY, B. A., M.B. Bombay: surgical registrar (casualty), Peterborough Memorial Hospital.
CHAUDHRY, J. K., M.B. Lucknow: surgical registrar, Ipswich and East Suffolk Hospital.
DAVIDSON, J. R. M., M.B. N.Z., F.R.C.S.E.: surgical registrar, Norfolk and Norwich Hospital.
MACKINTOSH, A. J., M.B. Glasg.: registrar in obstetrics and gynæcology, West Norfolk and King's Lynn General Hospital.

Oxford Regional Hospital Board:

HADFIELD, G. J., M.S. Lond., F.R.C.S.: consultant in general surgery, Aylesbury/High Wycombe area department of general surgery.
PRYER, R. R. L., M.B. Lond., F.R.C.S.: consultant in general surgery, Aylesbury/High Wycombe area department of general surgery.
SHRIBMAN, IRVING, M.B. Dubl., D.P.M.: consultant psychiatrist, St. John's Hospital, Stone.

Colonial Appointments:

ABAYOMI-COLE, A. B., O.B.E., M.B. Durh.: D.D.M.S., Sierra Leone.
EVANS, A. E. J., M.B. Lpool: M.O., Bahamas.
MCARDLE, J. M., M.B. Edin.: M.O., Uganda.
MURPHY, J. C. V., M.B. Lpool, D.T.M. & H., T.D.D.: M.O., Northern Rhodesia.
NARAIN, H. B., M.B.: M.O., Nigeria Northern Region.
THOMAS, G. M., M.D. Edin., M.R.C.P.E., D.P.H.: senior specialist, Hong Kong.
WALLING, K. E., M.B. St. And., D.P.H.: M.O.H., Mauritius.
WHIMSTER, W. F., M.B. Cantab.: M.O., Fiji.
YAP, PAO-MENG, M.D. Cantab., M.R.C.P.E., D.P.M.: senior specialist, Hong Kong.